

Amendments to the Drawings:

Figures 1 through 8 as originally filed have been deleted and Figures 9 through 17 have been renumbered accordingly. No new matter has been added.

Attachment: Replacement sheets (13 pages)
Annotated Marked-up Drawings (37 pages)

REMARKS

Claim Amendments

Claims 1 and 5 have been amended and Claim 7 has been canceled herein. Support for these amendments can be found throughout the specification and in the claims as originally filed. No new matter has been added.

Objections to the Drawings

The drawings have been objected to for containing sequences that are included in the sequence listing. Figures 1 through 8, providing the amino acid sequence and the nucleic acid sequence of various histone deacetylases, have been deleted herein. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-3 and 5 Under 35 U.S.C. §112, First Paragraph

Claims 1-3 and 5 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Specifically, the Office Action states that the specification as filed includes only antisense compounds that hybridize to the human form of histone deacetylase, however, the claims are not limited to the human-isotype specific antisense oligonucleotides as exemplified in the specification. Moreover, the Office Action states that the scope of the antisense compounds of the present invention includes those that hybridize to DNA or RNA of undefined length that “comprises” a region of undefined length of the sequence set forth in SEQ ID NO: 2.

Claim 1 has been amended to recite that the oligonucleotide inhibits the expression of one or more human histone deacetylase isoforms but less than all human histone deacetylase isoforms. The rejection is therefore rendered moot.

Additionally, Applicants disagree that the scope of the antisense compounds of the present invention includes those that hybridize to DNA or RNA of undefined length that “comprises” a region of undefined length of the sequence set forth in SEQ ID NO: 2. As defined in Claim 1, the oligonucleotides are from about 15 to about 26 nucleotides in length and as depicted in the sequence listing, SEQ ID NO 2 is 1611 nucleotides in length. In other words, the claimed oligonucleotides hybridize under physiological conditions to an about 15 nucleotide to about 26 nucleotide region of the 1611 nucleotides of SEQ ID NO 2.

One skilled in the art would clearly understand that Applicants had possession of the full scope of the antisense oligonucleotides encompassed by the instant claims. Reconsideration and withdrawal of the rejection are respectfully requested.

The Office Action also supports the written description rejection with language that appears to state that Applicants have not enabled the instantly claimed invention. Specifically the Office Action states that although the specification teaches the sequences of human histone deacetylase isoforms 1 through 8, a generic search of the term "histone deacetylase" in GenBank resulted in 263 hits for genes encoding a histone deacetylase. Additionally, the Office Action states that effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells. Applicants will address the comments accordingly.

A generic search for the term "histone deacetylase" in GenBank is a faulty search and although it resulted in 263 "hits", these hits were excessively repetitive and not indicative of 263 different human isoforms of histone deacetylase. To date, only 11 different isoforms of human histone deacetylase are known. However, even if there were 263 different human isoforms of histone deacetylase, Applicants are not required to specifically describe that which is already known. Applicants have provided enough guidance so that one skilled in the art would be able to take the sequence of any known histone deacetylase isoform from any species and come up with an antisense that meets the limitations of the claimed invention. *See Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1361 (Fed. Cir. 1998) ; *Engel Indus. Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir. 1991) [T]here is no requirement that the specification enable every mode for making and using the claimed products."; "The reason for such a rule is clear. What would be the value in patenting a composition at all if, by making the slightest alteration in the method of making what is nonetheless the same product, a competitor were able to evade liability? A patent system that permitted such conduct would remove the carrot dangling in front of the inventor's nose. If inventors were so easily divested of their limited monopoly rights attendant to their novel, useful, and nonobvious contributions, they would likely abandon their pursuits and thereby inhibit progress. The law does not permit such an outcome."

Moreover, even though effective antisense molecules must be found empirically by screening a large number of candidates, this does not necessarily make the experimentation

undue. Applicants respectfully submit that the specification accurately teaches how to practice the claimed invention. One skilled in the art could easily reproduce Applicants' results by simply following the examples and the disclosed oligonucleotides. As to other oligonucleotides, undoubtedly some screening using the methods disclosed in the specification and examples would be required. However, these experiments, which would require no modification of the disclosed assays, would not be undue. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *Massachusetts Institute of Technology v. A.B. Fortia*, 227 U.S.P.Q. 428 (Fed. Cir. 1985). In the antisense field, scientists typically engage in such screening, and would have to do so no matter how many oligonucleotides are exemplified. Applicants have clearly met this requirement.

Rejection of Claims 1-3 and 7 Under 35 U.S.C. §102(e)

Claims 1-3 and 7 are rejected under 35 U.S.C. §102(e) as being anticipated by Besterman et al. (US PAT No 6,953,783).

Claim 7 has been canceled herein, thus rendering the rejection moot as it applies to this claim. Additionally, Claim 1 has been amended to incorporate subject matter from pending Claim 5 thereby obviating this rejection as it applies to Claim 1 (and Claims 2-3 which are dependent on Claim 1). Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-3, 5 and 7 Under 35 U.S.C. §103(a)

Claims 1-3, 5 and 7 are rejected under 35 U.S.C. §103(a) as being unpatentable over Besterman et al. as applied to Claims 1-3 and 7 above, in view of Bennett et al.

The subject matter of Besterman et al. and the instantly claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person. Therefore, Besterman et al. does not preclude patentability under this section. The teachings of Bennett et al. do not render the instantly claimed invention obvious. Reconsideration and withdrawal of the invention are respectfully requested.

Provisional Double Patenting

Claims 1-3, 5 and 7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-11 of copending U.S. Application No. 10/870,587.

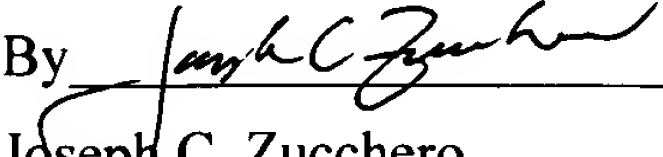
As stated by the Examiner, this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. If this provisional double patenting rejection is the only remaining rejection in this earlier filed application, Applicants request that the Examiner withdraw the rejection and allow this application to issue as a patent (See MPEP §804(I)(B)). Applicants will then consider filing a Terminal Disclaimer or take any other action deemed necessary in the later filed copending application.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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MAQTQGTRRKVCYYDGDVGNYYYGQGHMPKPHRIRMTHNLLN
YGLYRKMEIYRPHKANAEEMTKYHSDDYIKFLRSIRPDNMSEYSKQMQRFNVEDCPV
FDGLFEFCQLSTGGSVASAVKLNKQQTDAVWAGGLHHAKKSEASGFCYVNDIVLAI
LELLKYHQRVLYIDIDIHHGDGVEEAFTTDRVMTVSFHKYGEYFPGTGLRDIGAGK
GKYAVYPLRDGIDDES YEALFKPVMSKVMEMFQPSAVVLQCGSDSLSGDRLGCFNL
TIKGHAKCVEFVKSEFNLPLMLGGGYTIRNVARCWTYETAVALDTEIPNELPYNDYF
EYFGPDFKLHSPSNMTNQNTNEYLEKIKQRLFENLRMLPHAPGVQMQAIPEDAIPPEE
SGDEDEDDPKRISICSSDKRIACEEEFSDSEEEGEGGRKNSSNFKKAKRVKTEDEKE
KDPEEKKEVTEEEKTKEEKPEAKGVKEEVKLA (SEQ ID NO:1)

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ANNOTATED MARKED-UP
DRAWINGS

~~FIG. 1A~~

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1 atgtctgggg tctctgcccg ctggtgctgc tgttcccac tcggtcatcc tgagaacaca
61 gcctgagcgr ctctgtcact cggggtagac cacgcgggga ggcgagcaag atggcgcaga
121 cgcagggcac ccgaggaaa gtctgttact actacgacgg gatatgttga aattactatt
181 atggacaagg ccacccaatg aagcctcacc gaatccgcat gactcataat ttgctgctca
241 actatggtct ctaccgaaaa atggaaatct atcgccctca caaagccaat gctgaggaga
301 tgaccaagta ccacagcagat gactacatta aattcttgcg ctccatccgt ccagataaca
361 tgtcggagta cagcaagcag atgcagagat tcaacgttgg tgaggactgt ccagtattcg
421 atggcctgtt tgagttctgt cagttgtcta ctggtggttc tgtgggaagt gctgtgaaac
481 ttaataagca gcagacggac atcgccgtga attgggctgg gggcctgcac catgcaaaaga
541 agtccgaggg atctggcctc tgttacgtca atgatatcgt ctggccatc ctggaactgc
601 taaagtatca ccagagggtg ctgtacattg acattgatat taccatggt gacggcgtgg
661 aagaggcctt ctacaccacg gaccgggtca tgactgtgtc cttcataag tatggagagt
721 acttcccagg aactggggac ctacgggata cggggctgg caaagacaag tattatgctg
781 ttaactaccc gctccgagac gggattgatg acgagtccta tgaggccatt ttcaagccgg
841 tcatgtccaa agtaatggag atgttccagc ctagtgcgtt ggtcttacag tgtggctcag
901 actccctatc tggggatcgg ttaggttgct tcaatctatc tatcaaaagg cacgccaaagt
961 gtgtggaatt tgtcaagagc tttaacctgc ctatgctgat gctgggaggc ggtggttaca
1021 ccattcgtaa cgttgcccgg tgctggacat atgagacagc tgtggccctg gatacggaga
1081 tccctaataga gcttcccatc aatgactact ttgaatactt tggaccagat ttcaagctcc
1141 acatcagtcc ttccaatatg actaaccaga acacgaatga gtacctggag aagatcaaac
1201 agcgactggt ttgaagaacctt agaatgctgc cgcacgcacc tggggtccaa acgcaggcga
1261 ttcctgagga cggcatccct gaggagagtg gcgatgagga cgaagacgac cctgacaagc
1321 gcatctcgat ctgctcctct gacaaacgaa ttgcctgtga ggaagagtct tccgattctg
1381 aagaggaggg agagggggc cgcaagaact ctccaactt caaaaaagcc aagagagtca
1441 aaacagagga tgaaaaagag aaagaccacg aggagaagaa aggaatcacc gaagaggaga
1501 aaaccaagga ggagaagcca gaagccaaag ggtcaagga ggaggccaag ttggcctgaa
1561 tggacctctc cagctctggc ttcctgctga gtccctcacg ttctttccc c (SEQ ID NO:2)

~~FIG. 1B~~ Deleted

MAYSQGGKKCKVCYYDGDIGNYYYGQGHMPKPHRIRMTNLLL
NYGLYRKMEIYRPHKATAEEMTKYHSDEYIKFLRSIRPDNMSEYSKQMHIPFNVGEDCP
AFDGLFEFCQLSTGGSVAGAVKLNRRQQTDMAVNWAGGLHAKKYEASGFCYVNDIVLA
ILELLKYHQRVLYIDIDIHHRGDGVEEAFYTDRVMTVSFYGEYFPGTGLRDI GAG
KGKYYAVNFP MCDGIDDES YGQIFKPIISKVMEMYQPSAVVLQCGADSLSGDRLGCFN
LTVKGHAKCVEVVKTFNLP LMLGGGYTILRNVARCWTYETAVALDCEIPNELPYNDY
FEYFGPDFKLHISPSNMTNQNTPEYMEKIKQRLFENLRMLPHAPGVQMQAIPEDAVHE
DSGDEDEDPKRISIRASDKRIACDEEFSDSEDEGEGRNVADHKKGAKARIEED
KKETEDKKTDVKEEDKSKDNSGEKTDTKGTKSEQLSNP (SEQ ID NO:3)

~~FIG. 2A~~

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1 cgccgagctt tggcacctc tggcgggtgg taccgagcct tccgggcgcc ccctcctctc
61 ctcccaccgg cctggcccttc ccggcggggac tatcgccccc acgttttccct cagccctttt
121 ctctcccggc cgagccggcg cggcagcagc agcagcagca gcagcaggag gaggaaggccg
181 gtggcggcgg tggccgggga gcccatggcg tacagtcaag gaggcggcaa aaaaaggctc
241 tgctactact acgacggtga tattggaaat tattattatg gacaggggtca tcccatgaag
301 cctcatagaa tccgcatgac ccataacttg ctgttaaat ctggctttaca caggaaaatg
361 gaaatatata gggcccataa agccactgcc gaagaaatga caaatatcca cagtgatgag
421 tataatcaaat ttctacggtc aataagacca gataacatgt gtaggtatag taagcagatg
481 catatattta atgttggaga agattgtcca gcgtttgatg gactctttga gttttgtcag
541 ctctcaactg ggggttcagt tgctggagct gtgaagttaa accgaccaaca gactgatatg
601 gctgttaatt gggctggagg attacatcat gctaagaaat acgaagcatc aggatcctgt
661 tacgttaatg atattgtgct tgccatcctt gaattactaa agtattcatca gagagtctta
721 tatatcgata tagatatcca tcatgggtgat ggtgtcgaag aagcttttta tacaacagat
781 cgtgtaatga cggtatcatt ccataaatat ccatggtgat ggggaatcat ttcctggcac agggagacttg
841 agggatatg gtgctggaaa aggcataatt aggcaaatat tatgctgtca attttccaat gtgtgatggg
901 atagacgatg agtcatatgg gcagatatat gcagatatat aagcctatta cttcaagggt gatggagatg
961 tatcaacctt gtgctgtggt attacagtgt ggtgagtggt cttgagactg tgaatagactg
1021 ggttgtttca atctaacagt caaaggctcat gctaaatgtg gctaaatgtg tagaagtgtt aaaaactttt
1081 aacttaccat tactgatgct tggaggagggt tggccttgat tggtagacaa cccgtaaatgt tgcctcgatgt
1141 tggacatatg agactgcagt tggccttgat tggccttgat accagacttc aaactgcata ttagtccttc aaacatgaca
1201 gattactttg agtattttg agtattttg accagacttc taccgaaaag caagctattc caagctattc aggttgcgc
1261 aaccagaaca ctccagaata taccgaaaag taccgaaaag taccgaaaag taccgaaaag taccgaaaag taccgaaaag
1321 atgttacctc atgcacctgg atgcacctgg atgcacctgg atgcacctgg atgcacctgg atgcacctgg atgcacctgg
1381 gacagtgagg atgaagatgg agaatctcca agaatctcca agaatctcca agaatctcca agaatctcca agaatctcca
1141 aagcggatag cttgtgatga gaaaggagca gaaaggagca gaaaggagca gaaaggagca gaaaggagca gaaaggagca
1501 agaaatgtgg ctgattcataa gaaaggagca gaaaggagca gaaaggagca gaaaggagca gaaaggagca gaaaggagca
1561 gaaacagagg aaaaaaaac aaaaaaaac aaaaaaaac aaaaaaaac aaaaaaaac aaaaaaaac aaaaaaaac
1621 gaaaaaacag ataccaaaag ataccaaaag ataccaaaag ataccaaaag ataccaaaag ataccaaaag ataccaaaag
1681 tctcaccat ttcagaaaat ttcagaaaat ttcagaaaat ttcagaaaat ttcagaaaat ttcagaaaat ttcagaaaat
1741 gaagacttct ggcttcattt ggcttcattt ggcttcattt ggcttcattt ggcttcattt ggcttcattt ggcttcattt
1801 actttttcgt ttttgatttt ttttgatttt ttttgatttt ttttgatttt ttttgatttt ttttgatttt ttttgatttt
1861 aaatttcttt tctccaccat tctccaccat tctccaccat tctccaccat tctccaccat tctccaccat tctccaccat
1921 gtcaaaaaaa ctgatctatt ctgatctatt ctgatctatt ctgatctatt ctgatctatt ctgatctatt ctgatctatt
1981 aaaag (SEQ ID NO: 4)

FIG. 2B

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MAKTVAYFYDPDVGNFHYGAGHPMKPHRLALTHSLVLHYGLYKK
MIVFKPYQASQHDMCRFHSEDIYIDFLQRVSPNTMQGFTKSLNAPAVGDDCPVFPGLFE
FCSRYTGASLQGATQLNNKICDIANWAGGLHHAKKEEASGFCYVNDIVIGILELLKY
HPRVLYIDIDIHHGDGVQEA FYLTDRVMTVSFHKYGN YFFPGTGM YE V GAESGRYYC
LNVPLRDGIDDQSYKHLFQPVINQVVD FYQPTCIVLQCGADSLGCDRLGCFNLSIRGH
CECVEYVKSFNIPPLVLG GGGYTVRNVARCWTYETSL LVEEAI SEELPYSEYF EYFAP
DFTLHPDVSTRIENQSRQYLDQIRQTIFENL KMLNHAPSVQIHDVPADLLTYDRTDE
ADAEEERGPEENYSRPEAPNEFYDGDHDNDKESDVEI (SEQ ID NO: 5)

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ANNOTATED MARKED-UP
DRAWINGS

FIG. 3A Deleted

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FIG. 3B

1 ggaattcgcg gccgcggcgg gcgcgggagg gctccgcgcg gcaccatgge
61 caagaccgtg gcctatttct acgaccccca gctccactacg gagctggaca
121 ccctatgaag ccccatcgcc tggcatcgac agccatacca gtcctgcatc acggctctcta
181 taagaagatg atcgctcctca tacattgact tccctgcagag agccatattg aaggcttcac
241 ctccgaggac aatgccttca acgtaggcga gcgcattcct gcaaggaggca accagctga acaacaagat
301 caagagtctt cgttacacag gccattaaact tatgtcaacg acattgtgat tggcatcctg ccatggaagt ttgaggcctc
361 gttctgctcg cgttacacag gccattaaact tatgtcaacg acattgtgat tggcatcctg ccatggaagt ttgaggcctc
421 ctgtgatatc tatgtcaacg gccattaaact tatgtcaacg acattgtgat tggcatcctg ccatggaagt ttgaggcctc
481 tggcttctgc tgggtgctc tacattgaca ttggtgctga ggggttcaag ggaattact tactactgtc ttccaagcca
541 tcgggtgctc cctcactgac atgtatgaag gccattgag ttctaccaac atcgagtcac ccaaacatc cactggtgga
601 cctcactgac cctcactgac atgtatgaag gccattgag ttctaccaac atcgagtcac ccaaacatc cactggtgga
661 cacagggtgac cctgcgggat ttctaccac ttggtgctga ccaagcactt gctggtcctg catccgaggg gctggtgga
721 cctgcgggat ttctaccac ttggtgctga ccaagcactt gctggtcctg catccgaggg gctggtgga
781 ggtagtggac gcttccctat agtgaatac atcgagaaac ctgaagatgc accatattctg cagtagtcacg agaaactcacg
841 ctgtgatcga ttgtcaagagc ttgtgcccgc gcttccctat agtgaatac atcgagaaac ctgaagatgc accatattctg cagtagtcacg
901 ttgtcaagagc ttgtgcccgc gcttccctat agtgaatac atcgagaaac ctgaagatgc accatattctg cagtagtcacg
961 ttgtgcccgc gcttccctat agtgaatac atcgagaaac ctgaagatgc accatattctg cagtagtcacg
1021 gcttccctat agtgaatac atcgagaaac ctgaagatgc accatattctg cagtagtcacg
1081 cagcaccgcg ctgtgaaac agacttcctg aaactatagc gaaagcgat gtaaacgagc atccagatgt gccagacaat
1141 ctgtgaaac agacttcctg aaactatagc gaaagcgat gtaaacgagc atccagatgt gccagacaat
1201 agacttcctg aaactatagc gaaagcgat gtaaacgagc atccagatgt gccagacaat
1261 gaaagcgat gtaaacgagc atccagatgt gtaaacgagc atccagatgt gccagacaat
1321 gaaagcgat gtaaacgagc atccagatgt gtaaacgagc atccagatgt gccagacaat
1381 cactctcttg aagggtctga aagggtctga aagggtctga aagggtctga aagggtctga aagggtctga aagggtctga
1441 ggggcttttg cctgactcttg cctgactcttg cctgactcttg cctgactcttg cctgactcttg cctgactcttg cctgactcttg
1501 cctgactcttg cctgactcttg cctgactcttg cctgactcttg cctgactcttg cctgactcttg cctgactcttg cctgactcttg
1561 caaggatagc tatctgggac tatctgggac tatctgggac tatctgggac tatctgggac tatctgggac tatctgggac
1621 ttgcccctta ttcttcccct ttcttcccct ttcttcccct ttcttcccct ttcttcccct ttcttcccct ttcttcccct
1681 agacaaggac tgagattgac tgagattgac tgagattgac tgagattgac tgagattgac tgagattgac tgagattgac
1741 ccttgcttcc agggaaagatg agggaaagatg agggaaagatg agggaaagatg agggaaagatg agggaaagatg agggaaagatg
1801 ctgaatccca gatgatggga gatgatggga gatgatggga gatgatggga gatgatggga gatgatggga gatgatggga
1861 ctctcacttt tggctttatg tggctttatg tggctttatg tggctttatg tggctttatg tggctttatg tggctttatg
1921 atttttgtta cctttgatgg ttttagcggc gcgc (SEQ ID NO:6)

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4LAMKHQQELLEHQRKLERHRQEQELEKQHREQKLQQLKNEKG
KESAVASTEVMKMLQEFVLNKKKALAHPNLNHCISSCPXYWYGKTQHSSLDQSSPPQS
3VSTSYNHPVLGMYDAKDDFPLRKTASEP NLKLRSLKQKVAERRSSPLLRRKDGPPV
TALKKRPLDVTDSACSSAPGSGPSSPNNSSGSVAENGIAPAVPSIPAETSLAHRLLVA
REGSAAPPLYTSPSLPNITLGLPATGPSAGTAGQQDTERLTLPALQQRLSLFPGTHL
TPYLSTSPLERDGGAAHSPLLQHMVLLLEQPPAQAPLVTLGALPLHAQSLVGADRVSP
SIHKLRQHRPLGRTQSAPLPQNAQALQHLVIQQQHQQFLEKHKQQFQQQLQMNKIIP
KPSEPARQPESHPEETEEELREHQALLDEPYLDRLPQKEAHAQAGVQVKQEP IESDE
EEAEPPREVEPGQRQPSQELLFRQQALLLEQQRIHQLRNYQASMEAAGIPVSFGGHR
PLSRAQSSPASATFPVSVQEPPTKPRFTTGLVYDTMLKHQCTCGSSSSHPEHAGRIQ
SIWSRLQETGLRGKCECIRGRKATLEELQTVHSEAHTLLYG TNPLNRQKLD SKKLLGS
LASVFVRLPCGGVGVDSDTIWNEVHSAGAARLAVGCVVELVFKVATGELKNGFAVVRP
PGHHAESTPMGEFYFNSVA AAKLLQQR LSVSKILLIVDWDVHHGNGTQQAFYS DPSV
LYMSLHRYDDGNFFPGSGAPDEVGTGPGVGFNVNMAFTGGLDPPMGDAEYLA AFRTVV
MPIASEFAPDVVLASSGFDAVEGHPTPLGGYNLSARCFGYLTKQLMGLAGGRIVL ALE
GGHDLTAICDASEACVSALLGNELDPLPEKVLQQRPNANAVRSM EKVM EIH SKYWRCL
QRTTSTAGRSLIEAQTCENEEAETVTAMASLSVGVP AEKRPDEEPMEEEPPL (SEQ ID NO:7)

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ANNOTATED MARKED-UP
DRAWINGS

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FIG. 4A

FIG. 4B-1	FIG. 4B-2	FIG. 4B-3	FIG. 4B-4	FIG. 4B-5
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~~FIG. 4B~~

1 ggagggttggtg gggccgccgc cgcggagcac cgtccccgcc gccgcccagag cccgagccccg
61 agcccgcgca cccgccgcgc ccgccgccgc ccgccgccga acagcctccc agcctgggcc
121 cccggcggcg ccgtggccgc gtcccggctg ggcggagcgc cgcceagacc cgcgcgccgg
181 cgggtggcgg cgcaggctga ggagatgcgg cgcggagcgc cggagcaggg ctagagccgg
241 ccgccgccgc ccgccgcggt aagcgcagcc ccggcccgcc gccgcgggc cattgtccgc
301 cgcgcccccc gcgccccgcg cagcctgcag gcttggagc ccgcggcagg tggacgccgc
361 cggtcacac ccgccccgcg ccgccccgcg ggcggccggt gccagcgcctg gccgcgccgc
421 gtgggacccg ccggtcccca gggccgccgc gcccctctg gacctttcca cccgcgccgc
491 gaggcggctt cgcgccccgc cgcggggggcg caggttcatc tgcagaagcc agcggcgccg
541 tctcccggtg cggggccccc cccccccgag caggttcatc tgcagaagcc agcggcgccg
601 tctgttcaac ttgtgggtta cctggctcat cctggccttg gagcaggct cggcgcttga
661 acgtctgtga ccagccctc accgtcccgc tacttgtatg tgttggcggg agtttggagc
721 tcgttggagc tctcgtttcc gtggaaattt tgagccattt cgaatcactt aaaggagtgg
781 acattgctag caatgagctc ccaaagccat ccagatggac ttcttggccg agaccagcca
841 gtggagctgc tgaatcccgc ccgcgtgaac cacatgcccc gacagggtgga tgtggccacg
901 gcgctgcctc tgcaagtggc cccccggca gegccatgg accgcgcct ggaccaccag
961 ttctcactgc ctgtggcaga gccggccctg cgggagcagc agctgcagca ggagctcctg

~~FIG. 4B-1~~ Deleted

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121 gcgctcaagc agaagcagca gatccagagg cagatcctca tcgccgagtt ccagaggcag
 131 cagcagcagc tctcccgga cagcagaggc cagctccacg agcacatcaa gcaataacag
 141 gagatgctgg ccatgaagca ccagcaggag ctgctggaac accagcggaa gctggagagg
 201 caccgccagg agcaggagct ggagaagcag caccgggagc agaagctgca gcagctcaag
 261 aacaaggaga agggcaaaaga gaggccgctg gccagcacag aagtgaagat gaagttacaa
 321 gaatttgtcc agagaccctc gtaataaaaa tcaataaaaa gaaggcgctg gccaccgga atctgaacca ctgacttcc
 381 agagaccctc gtaataaaaa gtaataaaaa gtaataaaaa cagcacagtt cagcacagtt cagcacagtt cagcacagtt
 441 cccagagcgc gatgacttcc ctcttaggaa aacagcttct ctcctataac cagcacagtt cagcacagtt cagcacagtt
 501 gatgacttcc ctcttaggaa aacagcttct ctcctataac cagcacagtt cagcacagtt cagcacagtt cagcacagtt
 561 aagcagaaag tggccgaaag acggagcagc cccctgttac gaaccgaatc gaaccgaatc gaaccgaatc
 621 gtccactgctc taaaaaagcg ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat
 681 ggctccggac ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat tccgttggat
 741 gcgctccggc gaaggctcgg ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat
 801 gaaggctcgg ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat tccgttggat
 861 ggctcgcctg ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat tccgttggat
 921 acccttcccg ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat tccgttggat
 981 ctgagcacct ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat tccgttggat
 1041 atggtcttac ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat tccgttggat
 1101 cccctccacg ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat tccgttggat
 1161 cggcagcacc ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat tccgttggat
 1221 ctgagcacct ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat tccgttggat
 1281 tccagcagc ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat tccgttggat
 1341 cagccggaga ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat tccgttggat
 1401 gacgagccct ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat tccgttggat
 1461 cagggtgaag ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat tccgttggat
 1521 gagccgggac ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat tccgttggat
 1581 ctggagcagc ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat tccgttggat
 1641 atccccgtgt ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat tccgttggat
 1701 gccacccttcc ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat tccgttggat
 1761 gtgtatgaca ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat tccgttggat
 1821 gagcagccg ccagctcacc tccgttggat tccgttggat tccgttggat tccgttggat tccgttggat

FIG. 4B-2

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881 aaatgcgagt gcatccgcgg acgcaaggcc accctggaag agctacagac ggtgcactcg
941 gaagccacac ccctcctgta tggcacgaac ccctcaacc ggcagaaact ggacagtaag
001 aaacttctag gctcgtctgc ctccgtgttc gtccggctcc ctgcggtgg tgttgggtg
061 gacagtgaca ccataaggaa cgaggtgcac tcggcggggcagccgcct ggctgtgggc
121 tgcgtggtag agctggtctt caaggtggcc acaggggagc tgaataatgg ctttgctgtg
181 gtccgcccccc ctggacacca tgcgaggag gcttctgcag cagaggttga gcttgagcaa gacctcatc
241 tccgcggccg tggcagccaa tggcagccaa tggaaacggg accagcagg ctttctacag cgaccctagc
301 gtggactggg acgtgcacca tggtaacggg agacgctgag tacttggcgg ccttcagaac ggtggtaatg
361 gtccctgtaca tgtccctcca ccgctacgac gatgggaact tcttcccagg cagcggggct
421 cctgatgagg tgggcacagg gcccggcgtg ggtttcaacg tcaacacggc ttccaccggc
481 ggcctggacc ccccatggg agacgctgag tacttggcgg ccttcagaac ggtggtaatg
541 ccgatacgcca gcgagtttgc cccggatgtg ccggtgtgt catcaggctt cagatgccgtg
601 gagggccacc ccaccctct caccctctac tggggggtac aacttctccg ccagatgctt cgggtacctg
661 acgaagcagc tgatgggcct ggctggcggc cggattgtcc cggccctcga gggaggccac
721 gacctgaccg ccatttgcga cgcctcggaa gcatgtgtt gcatgtgtt ctgccctgct gggaaacgag
781 cttgatcctc tcccagaaaa ggttttagag caaagaccca atgcaaacgc tgtccgttcc
841 atggagaaag tcatggagat ccacagcaag tactggcgct gcctgcagcg cacaacctcc
901 acagcggggc gttctctgat ctaggctcag acttgcgaga acgaagaagc cgagacggtc
961 accgccatgg cctcgtctgc cgtggacgtg aagcccgccg aaaagagacc agatgaggag
021 cccatgggag aggagccgcg cctgtagcac tccctcgaag ctgctgttct cttgtctgtc
081 tgtctctgtc ttgaagctca gccaaagaaac ttcccgctgt caccctgctg tcccaccgtg
141 gggctctctt ggagcaccga gggacacca gcgtgcaaca gcacgggaa gccttctgc
201 cggccaggcc cacaggcttc gagacgcaca tgcacgcctg ggcgtggcag cctcacaggg
261 aacacgggac agacgcccgc gacgcgcaga cacacggaca cgcggaagcc aagcacactc
321 tggcgggtcc cgcaagggac gccgtggag aaaggagcct gtggcaacag gcggccgagc
381 tgccgaattc agttgacacg aggcacagaa aacaaatatc aaagatctaa taatacaaaa
441 caaacttgat taaaactggt gcttaagtt tattaccac aactccacag tctctgtgta
501 aaccactcga ctcatcttgt agcttatttt ttttttaag aggacgtttt ctacggctgt
561 ggcgccctc tgtgaacat agcgggtgtgc ggcgggggggt ctgcaccccg gtgggggaca
621 gagggacctt taaagaaac aaaactggac agaaacagga atgtgagctg ggggagctgg
681 cttgagtttc tcaaaagcca tcggaagatg cgagtgtgtg ccttttttt tattgctctg

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FIG. 4B-3

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741 gtggattttt gtggctgggt tttctgaagt ctgaggaaca atgccttaag aaaaacaaa
801 cagcaggaat cggtaggaca gtttccctgtg gccagccgag cctggcagtg ctggcacggc
861 gagctggcct gacgcctcaa ccctgttttg ctttatgtc gacggggcac aggggtgca
921 gccggcggt ccctgttttg ctttatgtc gtttatgtc gtttatgtc gtttatgtc
981 agtggcaaat ccgttggag gtttatgtc gtttatgtc gtttatgtc gtttatgtc
041 ctcacagtc acatagatt gagcatctcc gagcatctcc gagcatctcc gagcatctcc
101 ttgcagtggt acgatcggaa tgctttttat taagaaga gtttaaga gtttaaga
161 attttaggta taaataaata tatatatgta taatatatat taatatatat taatatatat
221 gaaacttact tgattcttat gaaatcttga taaatatatt taaatatatt taaatatatt
281 gtatatatat atataaaaa tgaatgcaga ttgcgaagg ttgcgaagg ttgcgaagg
341 tgaatttgct ctcaagggtgc ttatggaaag ggatccctgat ggatccctgat ggatccctgat
401 tcaagctcca gattggctag atttcagatc ggcaacacat ggcaacacat ggcaacacat
461 tacaagtttg tactttcatt ttaattattt ttaattattt ttaattattt ttaattattt
521 tcatgcacat atgtaccctaa tgagttttta tagcaaaagaa tagcaaaagaa tagcaaaagaa
561 ttgtatgaat tttttcacia aaagatcctg aataagcatt aataagcatt aataagcatt
641 ttccctcacca tttagcaatt ttccgaatgg taataatgtc taataatgtc taataatgtc
701 attcttgctt gtacattttt ttttaccctt caaagggttt caaagggttt caaagggttt
761 tttgtacgat gagttttctg cagcgtacag aattgttgct aattgttgct aattgttgct
821 agtgagagga gggaccgtag gtctttttcgg agtgacacca agtgacacca agtgacacca
881 ctgtccctagg agctgtataa agaagcccag gggctctttt gggctctttt gggctctttt
941 attacgagg gtgggtgtgtt ttcccccctcc ttgccagatg ttgccagatg ttgccagatg
001 gccgggccac cctgggaggc cctgggaggc atcgtcagga atcgtcagga atcgtcagga
061 gtttaaatc ctttgaccac ctttgaccac ctttgaccac ctttgaccac ctttgaccac
121 ttttgagcat gtcagcaatg catggggcac catggggcac catggggcac catggggcac
181 ccactgcagc cacgtggcca gccctggatt gccctggatt gccctggatt gccctggatt
241 accctgttg cctgggtgaac ctgcaggagg ctgcaggagg ctgcaggagg ctgcaggagg
301 tttactcttt ttctcttcaa cagtaactga cagtaactga cagtaactga cagtaactga
361 agcacatgaa gccaccagtt tcattccaaa tcattccaaa tcattccaaa tcattccaaa
421 agttcagaca caccgtgctc aggggggacc aggggggacc aggggggacc aggggggacc
481 tacagggtag cttctgaaat taactcaaac taactcaaac taactcaaac taactcaaac
541 tcaacttggtc actgggctgc tgatgggtcag ctctgagaca ctctgagaca ctctgagaca

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FIG. 4B-4

FIG. 4B-5

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601 acggtcttgg gacttgtttg actttccct cctggtggc cactcttgc tctgaagcc
661 agattggcaa gaggagtgg tccattcccc attcatggca cagaacagtg gcagggecca
721 gctagcaggc tcttctggcc tcttggcct ccttcttgc cattcttct atagccctct gggatcctg
781 ccacctgccc tcttaccctg cctgggctta cgtggaggaa tgcattcat tctttttt
841 ttttaagcag atgatgggat aacatggact aacatgggc gcttatca gtgggggac
901 ttaattctaa tctcattcaa atggagacga cctctgcaa ggcctggag gggaggcaa
961 gttcatctg ttagctcact ccagcttcac aatgtgctg agagcattac tgtgtagcct
021 tttctttgaa gacacactcg gctcttctcc acagcaagcg tccagggcag atggcagagg
081 atctgcctcg gcgtctgcag gcggaccac gtcaggagg gttccttcat gtgttctccc
141 tgtgggtcct tggaccttta gcctttttct tcttttgcaa aggccttggg ggcactggct
201 gggagtcagc aagcgagcac ttatatccc tttagaggaa accctgatga cgcactggg
261 cctcttggcg tctgacctgc cctgcctgct cccgctggt cgcagcgtg ccacgtgccc
321 cagccccac cagcaggcgg ctgccccgga ggcctggtg cgtgggact ggccgcccct
381 cccagcgtc ccagggtct tggaaatct gtttgcaagg ggaaggacca tttcgtaatg gtctgacaca
441 tttacttctt aaagcaagtt tgatttttgc agcactagca atggactttg ttgcttttct tttgatcag
501 aacattcctt tgggcccacg tgttttatgg cctacacctg gactgtacg ctttgggaa gatgggaaat tttctgtaaa
561 tgggcccacg ttttaagtct tatacagatt ttgcacgcca tgacatttg agggcggga agaaataa aaaggactac accaataa gagtttatg tatttatgtg
621 gaatacatct ttttaagtct tatacagatt ttgcacgcca tgacatttg agggcggga agaaataa aaaggactac accaataa gagtttatg tatttatgtg
681 gaatacatct ttttaagtct tatacagatt ttgcacgcca tgacatttg agggcggga agaaataa aaaggactac accaataa gagtttatg tatttatgtg
741 ctttatattg ttttatattg ttttaagtct tatacagatt ttgcacgcca tgacatttg agggcggga agaaataa aaaggactac accaataa gagtttatg tatttatgtg
7801 gcctttctgt ttttatattg ttttaagtct tatacagatt ttgcacgcca tgacatttg agggcggga agaaataa aaaggactac accaataa gagtttatg tatttatgtg
7861 acaaaacctt gaaggagagg gaaggagagg agggcggga agaaataa aaaggactac accaataa gagtttatg tatttatgtg
7921 aaattgtact ttttatattg ttttaagtct tatacagatt ttgcacgcca tgacatttg agggcggga agaaataa aaaggactac accaataa gagtttatg tatttatgtg
7981 gaaaaaaagt ttatatagca ttatatagca ttatatagca ttatatagca ttatatagca ttatatagca ttatatagca ttatatagca
3041 gaaacagtgt tttagggaat tttagggaat tttagggaat tttagggaat tttagggaat tttagggaat tttagggaat
3101 tgatttggag gaattttgtt gaattttgtt gaattttgtt gaattttgtt gaattttgtt gaattttgtt gaattttgtt
3161 gccaggcgag gccggcccgc gccggcccgc gccggcccgc gccggcccgc gccggcccgc gccggcccgc gccggcccgc
8221 ggggactcg aaagagtccc aaagagtccc aaagagtccc aaagagtccc aaagagtccc aaagagtccc aaagagtccc
8281 gtgatgtatg gctaagattt gctaagattt gctaagattt gctaagattt gctaagattt gctaagattt gctaagattt
8341 caattatact ttgcattcgaa ttgcattcgaa ttgcattcgaa ttgcattcgaa ttgcattcgaa ttgcattcgaa ttgcattcgaa
8401 ttagctcggc ctactttgt ctactttgt ctactttgt ctactttgt ctactttgt ctactttgt ctactttgt

ID NO:8)

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LRQGGTLTGKFMSTSSIPGCLLGVALEGDSPGHASLLQHVL

LEQARQQSTLIAVPLHGQSPLVTGERVATSMRTVGKLPRHRPLSRTQSSPLPQSPQAL

QQLVMQQHQQLLEKQKQQQLQLGKILTKTGELPRQPTTHPEETEEELTEQEVLLGE

GALTMPREGSTESESTQEDLEEEDEEEEDCIVKDEEGESGAEFGPDLEEPGA

GYKKLFSDAQPLQPLQVYQAPLSLATVPHQALGRQTSSPAAPGGMKSPDQPVKHLFT

TGVVYDTFMLKHQCMCGNTHVHPEHAGRIQSIWSRLQETGLLSKCERIRGRKATLDEI

QTVHSEYIHTLLYGTSPLNRQKLDKLLGPIQKMYAVLPCGGIGVDSDTVWNEMHSS

SAVRMAVGCLLELAFKVAAGELKNGFATIRPPGHAAEESTAMGFCFFNSVAITAKLLQ

QKLNVGKVLIVDWDIHHGNGTQQAFYNDPSVLYISLHRYDNGNFFPGSGAPEEVGGP

GVGYNVNAVWTGGVDPPIG DVEYLTAFRTVVMPIAHEFSPDVVTLVSAGFDAVEGHLSP

LGGYSVTARCEGHLTRQLMTLAGGRVVLALGGHDLTAICDASEACVSALLSVELQPL

DELVLQKPNINAVATLEKV IETQSKHWSCVQKFAAGLGRSLREAQAGETEEAETVSA

MALLSVGAEQAAAREHSPPRAEFPMEQEPAL (SEQ ID NO:9)

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FIG. 5A

FIG. 5B-1
FIG. 5B-2

~~FIG. 5B~~

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ANNOTATED MARKED-UP
DRAWINGS

1 ccctgaggca gggtaggacg ctgaccggca agttcatgag cacatcctct attcctgget
 61 gcctgctggg cgtggcactg gagggcgacg ggagcccca cgggcatgcc tccctgctgc
 121 agcatgtgct gttgctggag caggcccgcc agcagagcac cctcattget gtgccactcc
 181 acgggcagtc cccactagtg cccactagtg acgggtgaac gtgtggccac cagcatgagg acggtaggca
 241 agctcccgcg gcactcggcc ctgagccgca ctcagtcctc accgctgccc cagagtcccc
 301 agggcctgca gcagctggtc atgcaacaac agcaceagca gttcctggag aagcagaagc
 361 agcagcagct acagctgggc aagatcctca ccaagacagg ggagctgccc aggcagccca
 421 ccaccaccc tgaggagaca gaggaggagc tgacggagca gcaggaggtc ttgctggggg
 481 agggagccct gaccatgccc cgggagggct ccacagagag tgagagcaca caggagacc
 541 tggaggagga ggacgaggaa gaggatgggg aggaggagga ggattgcac caggttaagg
 601 acgaggaggg cgagagtggg gctgaggagg gcccgcactt ggaggagcct ggtgctggat
 661 acaaaaact gttctcagat gccacggccg tgcagccttt gcagggtgtac caggcgcccc
 721 tcaggcctggc cactgtgccc caccaggccc tgggcccgtac ccagtcctcc cctgctgccc
 781 ctggggggcat gaagagcccc ccagaccagc ccgtcaagca cctcttcacc acagggtgtg
 841 tctacgacac gttcatgcta aagcaccagt gcatgtgcgg gaacacacac gtgcaccctg

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~~FIG. 5B-1~~

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901 agcatgctgg ccggatccag agcatctggt cccggctgca ggagacaggc ctgcttagaa
961 agtgcgagcg gatccgaggt cgcaaaagcca cgctagatga gatccagaca gtgcaactctg
1021 aataccacac cctgctctac gggaccagtc cctcaaccg gcagaagcta gacagcaaga
1081 agttgctcgg ccccatcagc caccgtgtgg aatgagatgc actcctccag tgctgtggt atggcagtgg
1141 tggacagtga gctgcctgct ggagctggcc ttcaaggagg ctgcaggaga gctcaagaat ggatttgcca
1201 gctgcctgct ccatccggcc ccaggacac caactcctac aaactcctac agcagaagtt gaacgtgggc aaggtcctca
1261 tcatccggcc catcaccgca ggacattcac catgccaatg gcacccaggca ggcgttctat aatgacccct
1321 actctgtagc catcaccgca aaactcctac catgccaatg gcacccaggca ggcgttctat aatgacccct
1381 tcgtggactg ggacattcac catctctctg catcgtatg acaacgggaa ctctcttcca ggctctgggg
1441 ctgtgctcta ggttgggtgga ggttgggtgga ggaccaggcg tggggtacaa tgtgaacgtg gcatggacag
1501 ctctgaaga ggttgggtgga ccccccatt ccacgagttc tcacctgatg tggtcctagt ctccggccggg tttgatgctg
1561 gaggtgtgga ccccccatt ccacgagttc tcacctgatg tggtcctagt ctccggccggg tttgatgctg
1621 tgccattgac ccccccatt ccacgagttc tcacctgatg tggtcctagt ctccggccggg tttgatgctg
1681 ttgaaggaca tctgtctcct ctgggtggct actctgtcac cgccagatgt tttggccact
1741 tgaccaggca gctgatgacc ctggcaggcg gctgggctggt gctggccctg gagggagggc
1801 atgacttgac cgccattctg gatgcctctg aggccttggt ctgggctctg ctccagtgtag
1861 agctgcagcc ctgggatgag gcagtcttgc agcaaaagcc caacatcaac gcagtggcca
1921 cgctagagaa agtcatcgag atccagagca aacactggag ctgtgtgcag aagttcgccg
1981 ctgggtctgg ccggtccctg cgagaggccc aagcagggtga ggccgaggag gccgagactg
2041 tgaggcccat ggccttgctg tcggtggggg ccgagcaggc ccaggctgctg gcagcccggg
2101 aacacagccc caggccggca gaggagcca tggagcagga gcctgccctg tgacgccccg
2161 gccccatcc ctctcggctt caccattgtg attttgttta tttttcttat taaaaacaaa
2221 aagtcacaca ttc (SEQ ID NO:10)

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FIG. 5B-2

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1 mtstgqdstd trqrrsrqnp qspqgdssvt skrnikkjav prsipnlaev kkkgkmkklg
61 qameedlivg lqgmdlnlea ealagtglvl deqlnefhcl wddsfpegpe rlhaikeqli
121 qeglldrcvs fgarfaekee lmlvhsleyi dlmettgymn egelrvladt ydsvylhpns
181 yscacclasgs vlrlvdavlg aeirngmai rppghhaqhs lmdgycmfnd vavaaryaqg
241 khrrrvliv dwdvhhgqgt qftfdqdpv lyfsihryeq grfwphlkas nwsttgfgqg
301 qgytinvpwn qvgmrdadyi aafhlvllpv alefqpqlvl vaagfdalqg dpkgemaatp
361 agfaqlthll mglaggklil sleggynira laegvsaslh tllgdpcpml espgapcrsa
421 qasvscalea lepfwevlvr stetverdnm eednveesee egpweppvlp iltwpvlqsr
481 tglvydqnmn nhcnlwdshh pevprilri morleelgia grcltityprp ateaelltch
541 saeyvghlra tekntrelh ressnfdsiy icpstfacaq Iatgaacrly eavisgevin
601 gaavvrppgh haeqdaacgf cffnsavava rhagtisgha lrilivdwdv hhngtqhmf
661 eddpsvlyvs lhrydhgtff pmgdegassq igraagtgt vnvawngprm gdadylaawh
721 rlvlpiafef npelvlvsag fdaargdplg gcqvspgya hlthllmgl sgrilileg
781 gynltsises maactrsilg dppplltlpr pplsgalasi tetiqvhrry wrslrvmkve
841 dregpssskl vtkaapapak prlaermtrr ekkvleagmg kvtsasfgee stpgqtnset
901 avvalcqdpq seaatggatl aqtiseaaig gamlgqttse eavggatpdpq ttseetvgga
961 ildqttseda vggatigqtt seeavggatl aqtiseaame gatldqttse eapggtelig
1021 tplasstdhq tpptspvqgt tpqispstli gslrtlelgs esqgasesqa pgeenllgea
1081 agggdmadsm lmqgsrgltd qai fyavtpl pwcphlvavc pipaagldvt qpcgdcgtiq
1141 enwvclscyq vycgryingh mlqhhgnsgh plvlsyidl s awcyycqayv hhqalldvkn
1201 iahqnkfged mphph (SEQ ID:11)

FIG. 6A Deleted

FIG. 6B-1	
FIG. 6B-2	
FIG. 6B-3	

~~FIG. 6B~~

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ANNOTATED MARKED-UP
DRAWINGS

~~1 gggcagtccc ctgaggagcg gggctggttg aaacgctagg ggcgggatct ggcggagtgg
61 aagaaccgcg gcaggggcca agcctcctca actatgacct caaccggcca ggattccacc
121 acaaccaggc agcgaagaag taggcagaac cccagtcgc ccctcagga ctccagtgtc
181 acttcgaagc gaaatatataa aaaggagcc gttccccgct ctatcccaa tctagcggag
241 gtaagaaga aaggcaaat gaagaagctc ggccaagcaa tggagaaga cctaatacgtg
301 ggactgcaag ggatggatct gaacctcgag gctgaagcac tggcttgggtg
361 ttggatgagc agttaaatga attccattgc ctctgggatg acagcttccc ggaaggccct
421 gagcggctcc atgccatcaa ggagcaactg atccaggagg gcctccctaga tcgctgcgtg
481 tcctttcagg cccggtttgc tgaaaaaggaa gagctgatgt tggttcacag cctagaatat~~

~~FIG. 6B-1~~ ~~DELETED~~

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FIG. 6B-2

541 attgacctga tggaaacaac ccagtacatg aatgaggag aactccgtgt ctagcagac
601 acccagact cagtttatct gcataccgaac tcatactcct gtgcctgcct gccctcaggc
661 tctgtcctca ggctggtgga tgcggtcctg ggggtgaga tccggaacgg catggccatc
721 attaggcctc ctggacatca cgccagcac agtcttatgg atggctattg catgttcaac
781 cacgtggctg tggcagcccg ctatgctcaa cagaacacc gcacccggag ggtccttatc
841 gtagattggg atgtgcacca atgtgcacca cggtcaagga acacagttca ccttcgaca ggacccagt
901 gtcctctatt tctccatcca ccgctacgag cagggtaggt tctggcccca tctggaaggc
961 tctaactggt ccaccacagg ttctggccaa ggccaaggat ataccatcaa tgtgccttgg
021 aaccagggtg ggatgcggga tgctgactac attgctgctt ctggtggccg ctggatttga cctgctgcca
081 gtcgccctcg agctccagcc tcagctggtc ctggtggccg ctggatttga tggcctgcaa
141 ggggacccca agggcgagat ggccgccact caagctgac ctgtctctgg aggtgggta caacctccgc
201 ctcatgggtc tggcaggagg caagctgac ctgtctctgg aggtgggta caacctccgc
261 gccctggctg aaggcgtcag tgcttcgctc caccacctc cagtttcttg agaccgtgga gagggacaac
321 ccggagtcac ctggtgcccc ctgccggagc gcccaggctt cagtttcttg agaccgtgga gagggacaac
381 gcccttgagc ccttctggga ggttcttctg agatcaactg agaccgtgga cctgggagcc cctgtgctc
441 atggaggagg acaatgtaga ggagagcgag gaggaaggac cctgggagcc cctgtgctc
501 ccaatcctga calggccagt gctacagctc cgcacagggc cgtcttatga ccaaaatag
561 atgaatcact gcaacttgtg ggacagccac caccctgagg taccctcagg catcttgagg
621 atcatgtgcc gtctggagga gctgggcctt gccgggagct gacctacct agtacgtggg tcatctccgg
681 cctgccacag aggtgagct gctcacctgt caccctgctg caccctcagg gttccaaact tgaactccatc
741 gccacagaga aaatgaaac ccgggagctg cagcttgcca cagcttgcca ctggcgctgc ctggcgctg
801 tatatctgcc ccagtacct tgetctcagg agaggctcctg aatggtgctg ctgtggctgcg tccccagga
861 gtggaggctg tgetctcagg agaggctcctg aatggtgctg ctgtggctgcg tccccagga
921 caccacgcag agcaggatgc agcttgctgt ttttgctttt gccctacgga tccctgattgt ggattgggat
981 gctcgccatg ccagactat cagtgggcat cagtgggcat gccctacgga tccctgattgt ggattgggat
1041 gtccacccacg gtaatggaac tcagcacatg tttgaggatg acccagtggt gctatatgtg
1101 tccctgcacc gctatgatca tggcaccttc tccccatgg gggatgaggg tggcagcagc
1161 cagatcgcc gggccgccc cacaggcttc accgtcaacg tggcatggaa cgggccccgc
1221 atgggtgatg ctgactacct agctgcctgg catcgccctg tgcttcccat tgcctacgag
1281 tttaaccag aactggtgct ggtctcagct ggctttgatg ctgcacgggg gatccgctg

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Deleted

FIG. 6B-3

341 gggggctgcc aggtgtcacc tgagggttat gccaccta cccacctgct gatgggcctt
401 gccagtggcc gcattatcct taccctagag ggtggctata acctgacatc catctcagag
461 tccatggctg cctgcactcg cctccctcctt ggagaccac ggagaccctt gacctgcca
521 cggcccccac tatcagggc gcttacgggt catgaaggca aaacctaggt tagctgagc gatgaccaca
581 tactggcgca agaaggcacc ccaaccagcc agcaggcatg gggaaagtca cctcggcatc atttggggaa
641 ttggtcacca agaggcacc ccaaccagcc taactcagag acagctgtgg tggcctcac tcaggaccag
701 cgagaaaaga aggttctgga agcaggcatg gggaaagtca cctcggcatc atttggggaa
761 gagtccactc cagggcagac taactcagag taactcagag acagctgtgg tggcctcac tcaggaccag
821 ccctcagagg cagccacagg gggagccact gggagccact ctggcccaga ccatctctga ggcagccatt
881 gggggagcca tgctgggcca gaccacctca gggagggctg gaggaggc accagaccac cactccggac
941 cagaccacct gagggagac cagaggagac gggagggga gggagggga gggagggga ggcagggat
001 gctgttggg gagccacgct gggcagact gggcagact gggcagact gggcagact gggcagact
061 ctggcccaga ccatctcgga cagggagac cagggagac gggagggga gggagggga gggagggga
121 gaggaggctc cagggggcac cagggggcac cagggggcac gggagggga gggagggga gggagggga
181 cagacccccc caacctcacc tggtcagggga gggagggga gggagggga gggagggga gggagggga
241 attgggagtc tcaggacctt gggagggga gggagggga gggagggga gggagggga gggagggga
301 gcccaggag aggaacacct accaggagag accaggagag accaggagag accaggagag
361 atgctgacgc agggatctag gggcctcact gggcctcact gggcctcact gggcctcact gggcctcact
421 ctgcccctggt gtcccattc ggggggactg ggggggactg ggggggactg ggggggactg ggggggactg
481 acccaacctt ggggggactg ggggggactg ggggggactg ggggggactg ggggggactg ggggggactg
541 caggtctacc gtggtcgtta catcaatggc catcaatggc catcaatggc catcaatggc catcaatggc
601 caccgcctgg tcctcagcca catcagacctg catcagacctg catcagacctg catcagacctg catcagacctg
661 gtccaccacc aggtctctcct agatgtgaag agatgtgaag agatgtgaag agatgtgaag agatgtgaag
721 gatagaccac acccacta acccacta acccacta acccacta acccacta acccacta acccacta
781 gatagaccac acccacta acccacta acccacta acccacta acccacta acccacta acccacta
841 atcccatcct gaatacctt tgcaactccc tgcaactccc tgcaactccc tgcaactccc tgcaactccc
901 taagagaact gcgacgatta attgtggatc attgtggatc attgtggatc attgtggatc attgtggatc
961 cactactcc agccagaag gaaagggggg gaaagggggg gaaagggggg gaaagggggg gaaagggggg
1021 tcatgaggat aacattggcg ggaggggagt taactggcag cagctcagtg gcccagaag ggagccgata
1081 taataaagta caagctgtt (SEQ ID NO: 12)

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1 mdlrvqgrpp vepppeptll alqrpqrllhh hlflaglqqq rsvepmrlsm dtpmpelqvg
61 pgeqelrqll hkdkskrsav assvkvkqla evilkqqaa lertvhpnsip gipyrtlepi
121 etegatrsmll ssflppvpsi psdpppehfp1 rktvsepnlk lrykpkksle rrknpllrke
181 sappslrrrp aetlgdssps ssstpasgcs spndsehgpn pilgdsdrrt hptlgprgpi
241 lgsphhtplfl phglepeagg clpsrlqpil lldpsgshap lltvpglgpl pfhfaqsimt
301 terlsqsglh wplsrtrsep lppsatappp pppmqrleq lkthvqvikr sakpsekpri
361 rqipseaedle tdgggpggvv ddglehrelg hqqpeargpa plqqhqvii weqqlagrl
421 prgstgdcvi lplaqqghrp lsraqsspa pasisapapa sqarvlssse tpartlpflt
481 gliydsvmllk hqscgdnr hpehagriqs iwsrlqergl rsqceclgr kasieelqsv
541 hserhvllyg tnplsrlkl ngklagialq rmfemlpcgg vgvdtatiwn elhssnaarw
601 aagsvtdlaf kvasreikng favvrppghh adhstangfc ffnsvaiacr qlqqskask
661 askilivdwd vnhgngtqqt fyqdpvlyi slhrhddgnf fpgsgavdev gagsgegfnv
721 nvawaggldp pmgdpeylaa frivvmpiar efspdlvls agfdaaeghp aplggyhvsa
781 kcfgymtqql mnlaggavvl alegghdlt a icdaseacva allgnrvdpl seegwkqkpq
841 pqchplsgr dpgaq (SEQ ID NO:13)

FIG. 7A DELETED

FIG. 7B-1	FIG. 7B-2
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FIG. 7B

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DELETED

FIG. 7B-1

1 ataataccta ccttgacgga ccacgacagg ataatgtgag gaaaaacccc catgagagtg
61 ttttgccatt gtcaagttag cctgagggag gctgaggggg gatcagggtg tatcatgccc
121 ccgaggacaa actttccagt ttaccctgct cctctctct agcccatgga gtccttaggc tgcccaggc
181 cctgcgcaga cacaccaggc cctcagccgc cctgcgggtg ggcagcggc
241 cccagtgga gcccaccaca gaggccacat tgctggcct gcagcgtccc cagcgcctgc
301 accaccacct ctccctagca ggcctgcagc agcagcgtc ggtggagccc atgaggctct
361 ccatggacac gccgacgccc gagtgcagg tgggacccca ggaacaagag ctgcggcagc
421 ttctccacaa ggacaagagc aagcgaagt ctgtagccag cagcgtggtc aagcagaagc
481 tagcggaggt gattctgaaa aaacagcagg cggccctaga aagaacagtc catcccaaca
541 gccccggcat tccctacaga acccggagc ccctggagac ggaaggagcc acccgctcca
601 tgctcagcag ccttcgcct cctgctcca gccgcccag tgaccccca gagcactccc
661 ctctgcgcaa gacagtctct gagcccaacc tgaagctgag ccataagccc aagaagtccc
721 cggagcggag gaagaatcca ctgctccgaa aggagagtgc gcccaccag ccccgggcgc
781 ggcccgcaga gacctcga gactcctccc caagtagtag cagcacgccc gcatcagggc
841 gcagtcccc caatgacagc gagcacggcc ccaatccat cctgggagac agtgaccgca
901 ggaccatcc gactctggc cccgggggc caatcctggg gagcccccac actcccctct
961 tcctgcccc tggttggag cccgaggctg ggggcacctt gccctcccgc ctgcagccca
1021 ttccctctct ggacccctca ggctctcatg cccgctgct gactgtgccc gggcttgggc
1081 ccttgccct ccaacttgcc cagtccttaa tgaccaccga gcggctctct gggtcaggcc
1141 tccactggcc actgagccgg actcgtcag agcccctgcc cccagtgcc accgctcccc
1201 caecgccggg ccccatgcag cccgcctgg agcagctcaa aactcacgtc caggatgaca
1261 agaggtcagc caagccgagt gagaagccc ggctgcggca gataccctcg gctgaagacc
1321 tggagacaga tggcggggga ccgggccagg tggtagcga cggccggag cacaggagc

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DELETED

FIG. 7B-2

381 tgggccatgg gcagcccgag gccagaggcc ccgctcctct ccagagcac cctcaggtgt
141 tgctctggga acagcagcga ctggctgggc ggctcccccg gggcagcacg ggggacactg
501 tgctgcttcc tctggcccag ggtgggcacc ggctctgtc ccgggtcag tcttccccag
561 ccgcacctgc ctactgtca gcccagagc ctgccagcca ctgccagtc ctctccagct
621 cagagacccc tgccaggacc ctgcccttca ccacagggtt gatctatgac tcggtcatgc
681 tgaagcacca gtgctcctgc ggtgacaaca gtcagcaccc ggagcacgcc ggcgcacatcc
741 agagcatctg gtcccggctg caggagcggg ggcctcggag ccagtgtgag tgtctccgag
801 gccggaaggc ctccctggaa gagctgcagt cggctccactc tgagcggcac gtgctcctct
861 acggcaccaa ccgctcagc cgcctcaaac ggcacaacgg gaagctggca gggctcctgg
921 cacagcggat gtttgagatg ctgccctgtg gtgggttgg ggtggacact gacaccatct
981 ggaatgagct tcattccLcc aatgcagccc gctgggcccg tggcagtgtc actgacctcg
041 ccttcaaagt ggcttctcgt gagctaaaga atggtttcgc tgtgggtgcgg ccccaggac
101 accatgcaga tcattcaaca gccatgggct tctgcttctt caactcagtg gccatcgcct
161 gccggcagct gcaacagcag agcaaggcca gcaaggccag gcaacctcta ccaagacccc agtgtgctct
221 gggacgtgca ccatcgccat gacgacggca acttcttccc ggggagtggg gctgtggatg
281 acatctccct tggcagcggg gagggcttca atgtcaatgt ggcctgggct gatagtcgtg acgcccacatc
341 aggtaggggc tggcagcggg gagggcttca atgtcaatgt ggcctgggct gatagtcgtg acgcccacatc
401 acccccccac tggcagcggg gagggcttca atgtcaatgt ggcctgggct gatagtcgtg acgcccacatc
461 ccgagagtt ctctccagac ctactgttt taccatgttt ctgccaaatg tggctgcttca atgtgaggtc
521 acccgcccc acLgggtggc taccatgttt taccatgttt ctgccaaatg tggctgcttca atgtgaggtc
581 aactgatgaa cctggcagga ggcgcagtgg tggctggcctt tgctggcctt ggcctgggtaac aggttggatc
641 cagccatctg tgacggcctct gaggcctgtg aaacagaaac ccaacctca atgcccactc ctctctggag
701 ccctttcaga agaaggctgg taaatactgg ggctgcatgc agcgccctggc ctccctgtcca
761 gccgtgatcc ggggtgcacag taaatactgg ggctgcatgc agcgccctggc ctccctgtcca
821 gactcctggg tgcctagagt gccaggggct gacaaagaag aagtggaggc agtgaccgca
881 ctggcgtccc tctctgtggg catcctggct gaagataggc cctcggagca gctgggtggag
941 gaggaagaac ctatgaatct ctaaggctct ggaaccatct gcccggccac catgcccttg
3001 ggaacctggt ctcttctaac ccctggcaat agccccatt cctgggtctt tagagatcct
3061 gtgggcaagt agttggaacc agagaacagc ctgcctgctt tgacagtatt cccagggagc
3121 gtgagaaaat c (SEQ ID NO:14)

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1 meepeepads gqslvpvviy speyvsmcde lakipkrasm vhsli~~ea~~yal ~~hkqmrivkpk~~
61 vasmeeematef htdaylqhlq kvsqegdddh ~~pdsieyglgy~~ dcpategifd yaaaiaggati
121 taaqclidgm ckvainwsgg whb~~ak~~deas gfcylndavl gilrlrrkfe rilyvdlldlh
181 hgdgvedafs ftskym~~te~~vsI hkfspgffpg tgdvsdvglg kgryysvnpv iqdgigdeky
241 yqicesvllke vyqafnpkav vlqlgadtia gdpmcdfnmt pvgigkclky ilqwqlatli
301 lgggynlan tarcwtyltg vilgktsse ipdbefftay gpdyvleith scrpdrneph
361 riqqilnyik gnlkhvv (SEQ ID NO:15)

~~FIG. 8A~~ Deleted

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1 gaaattcggc acgagctcgt gccgaattcg gcacgagaac ggttttaagc ggaagatgga-
61 ggagccggag gaaccggcgg acagtgggca gtcgctggtc ccggtttata tctatagtcc
121 cgagtatgtc agtatgtgtg actccctggc caagatccc atagtttaagc gtatggtgca
181 ttctttgatt gaagcatatg cactgcataa gcaaatgagg tgatgcttat ccagaagggt
241 ctccatggag gagatggcca cctccacac ctccatagaa tatgggctag gttatgactg
301 cagccaagag ggcgatgatg atcatccgga ctccatagaa ggaggggcta cgatcacagc
361 ccagccact gaaggatat tgactatgc gaatgtgcaa agtagcaatc aactggtctg gaggtggca
421 tgcccaatgc ctgattgacg catctgggtt tcgttatctc aatgatgctg tcctgggaat
481 tcatgcaaa aaagatgaag ttgagcgtat tccctacgtg gattcggatc tgcaccatgg
541 attacgattg cgacggaaat tcagtttcac ctccaaagt atgaccgtgt ccctgcacaa
601 agatgggtga gaagacgcat tgagtttcac caggaacagg tgacgtgtcc gacgttggcc tagggaagg
661 attctccca ggatttttcc tgcccatcca gcatggcata caagatgaaa aatatacca
721 acggtactac agtgtaaatg aggaagtata ccaagccttt aatcccaaag cagtgggtctt
781 gatctgcgaa agtgtaactaa tagctgggga tccatgtgc tcctttaaca tgactccagt
841 acagctggga gccgacacaa agtaaatccc tcaatggcag ttggcaacac tcatttcggg
901 gggaattggc aagtgtctca agtaaatccc tcatgctgg acatactga ccggggtcat
961 aggaggaggc tataaccttg ccaacacggc tcgagtctgg tttttcacag catatggtcc
1021 cctagggaaa aactatcct ctgagatccc agatcatgag tttttcacag ccacccgaat
1081 tgattatgtg ctggaaatca cgccaagctg tctgaagcat gtggtctagt tgacagaaag
1141 ccaacaaatc ctcaactaca tcaaagggaa cctataatga agacagcgtg ttatgcaag
1201 agatcagggt tcaagagctg aggagtgggtg atttgaaaga aattacttcc tgaaaaattc
1261 cagtttgrgg aatttgtgac tgcagggaaa ctggcttcct ggggtgaaga ggcaggcacc
1321 caaggggcat caagtggcag ctggcttcct ccaactttaa agttcttatt taaaaaaca
1381 caactggacc taggggaaga aggagatarc aaacttattt ttaagcgaat tggggagggt
1441 cacacacaca aatgaaattt ttaacttttg cagaagctgg atgagagcag tcaccagt
1501 agtattttaa tcatcttaa aggagctga tngggcctcn ggaccancca ngtgaggccc
1561 gtagggcagg aggcagctga caggcagggn tngggcctcn ggaccancca ngtgaggccc
1621 tgggagagan ggtactgatc ngcagactgg gagg (SEQ ID NO:16)

FIG. 8B

~~25/37~~ 1/13

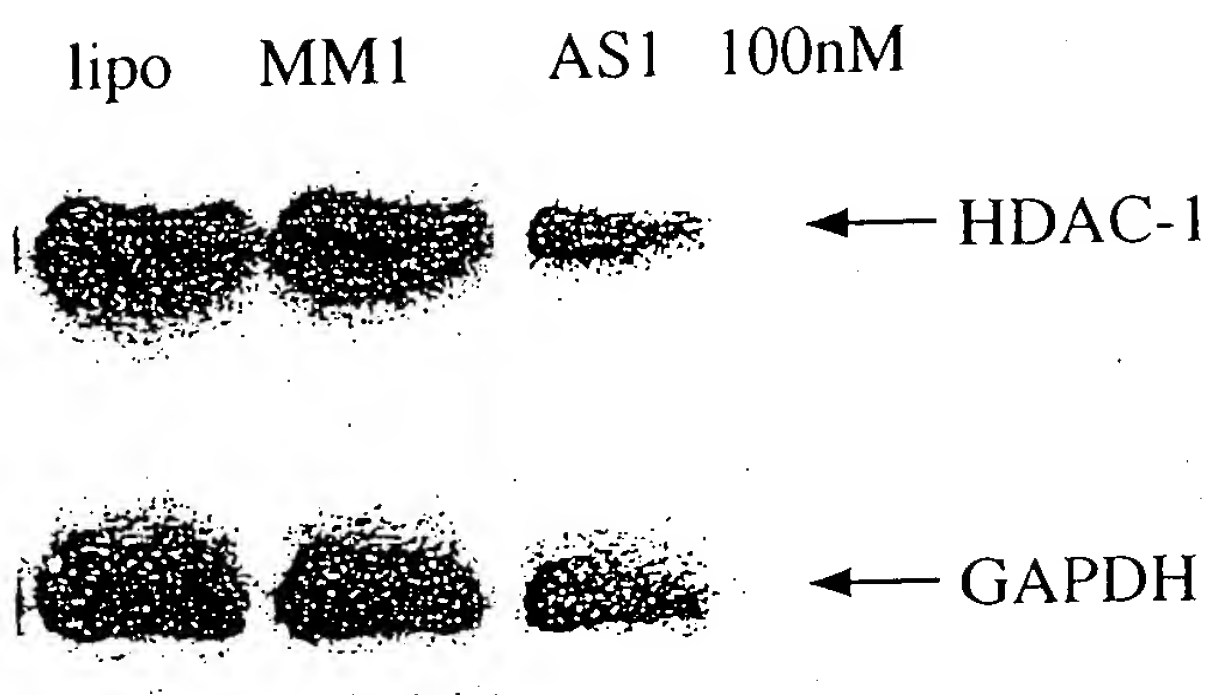


FIG. 9A 1A

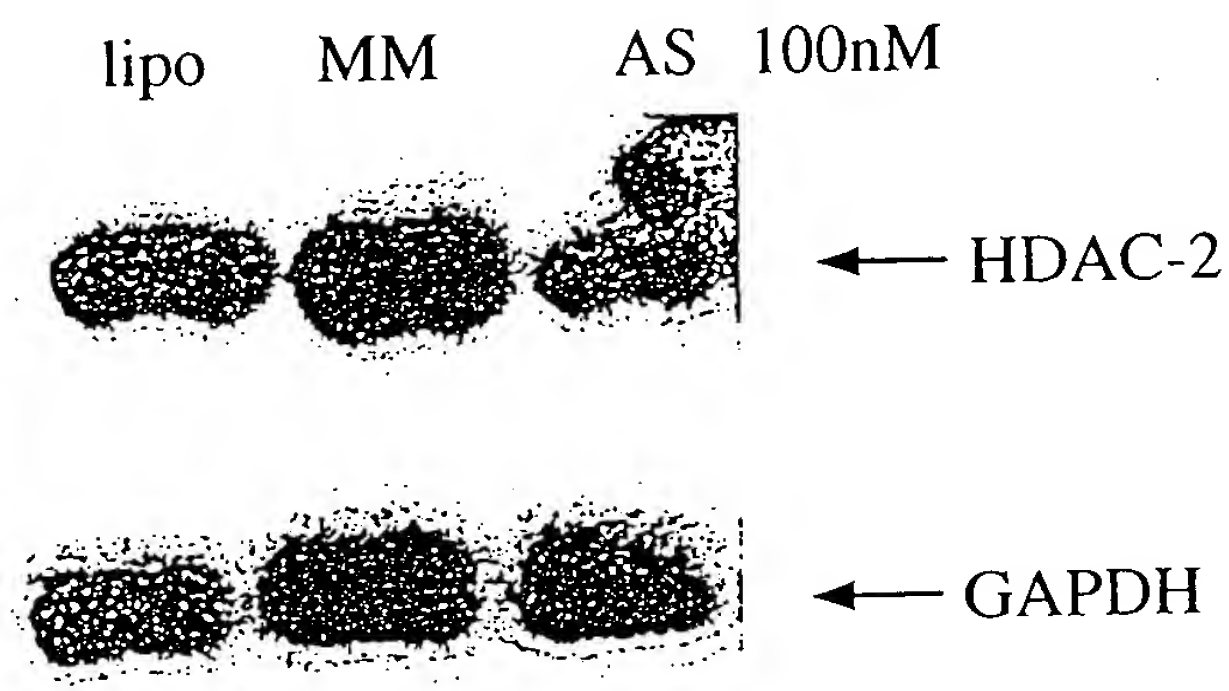


FIG. 9B 1B

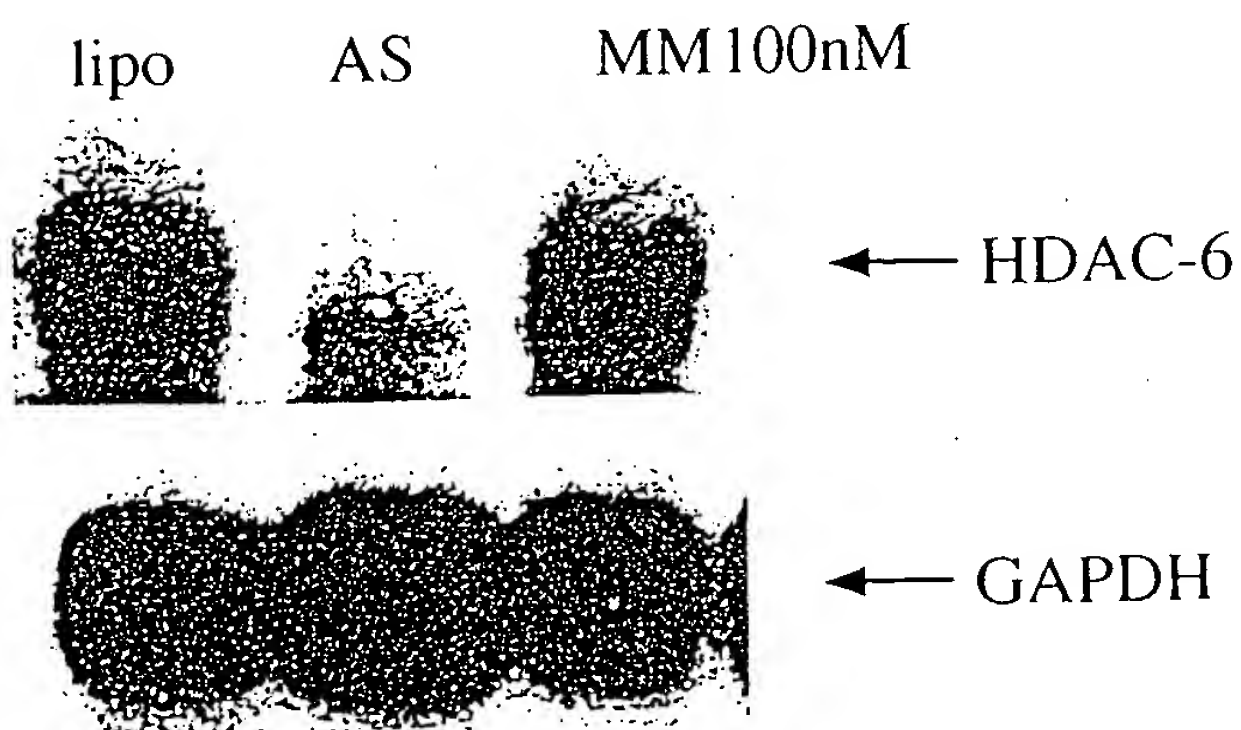


FIG. 9C 1C

~~26/37~~ 2/13

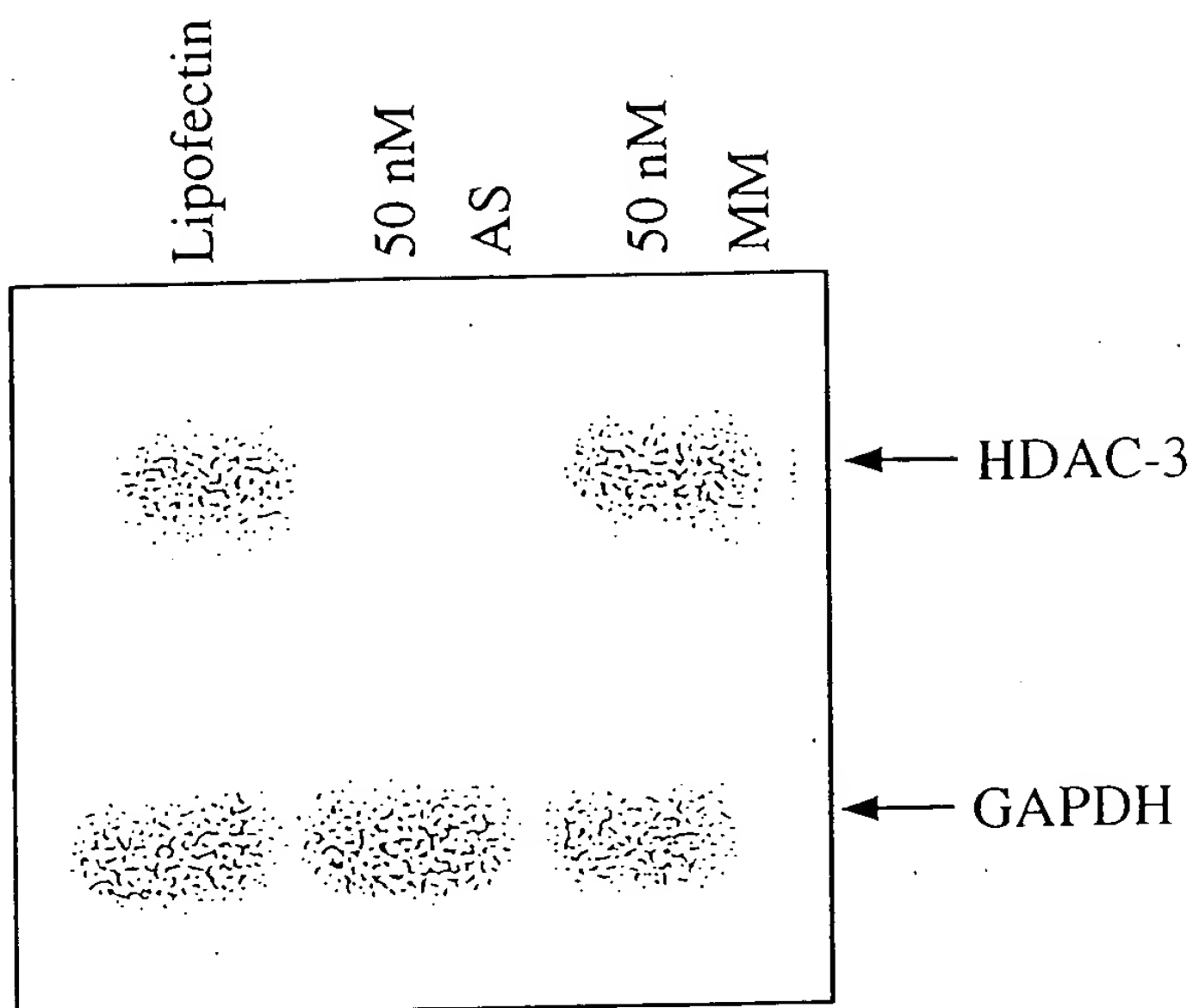


FIG. 9D 1D

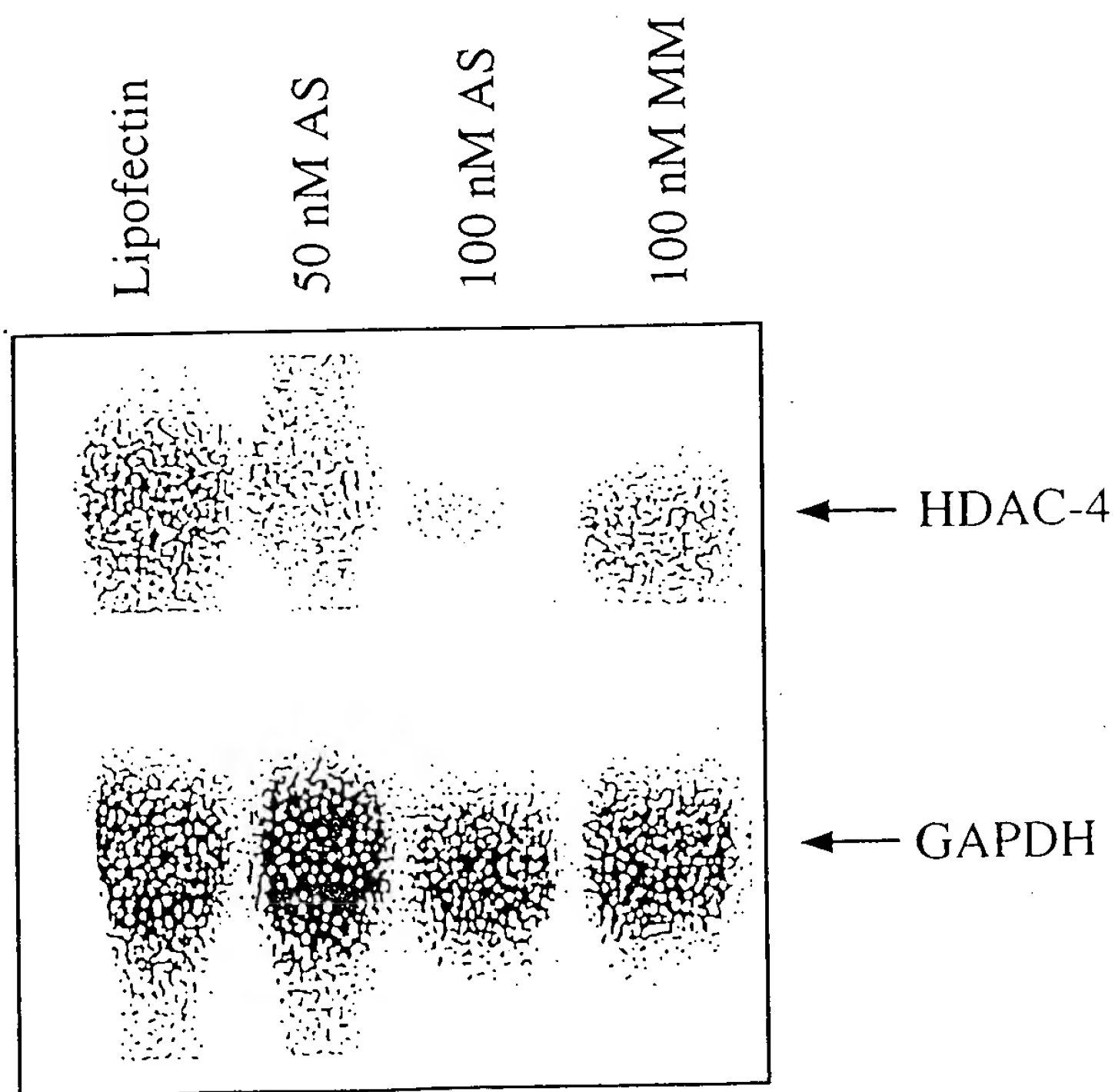


FIG. 9E 1E

~~27/37~~ 3/13

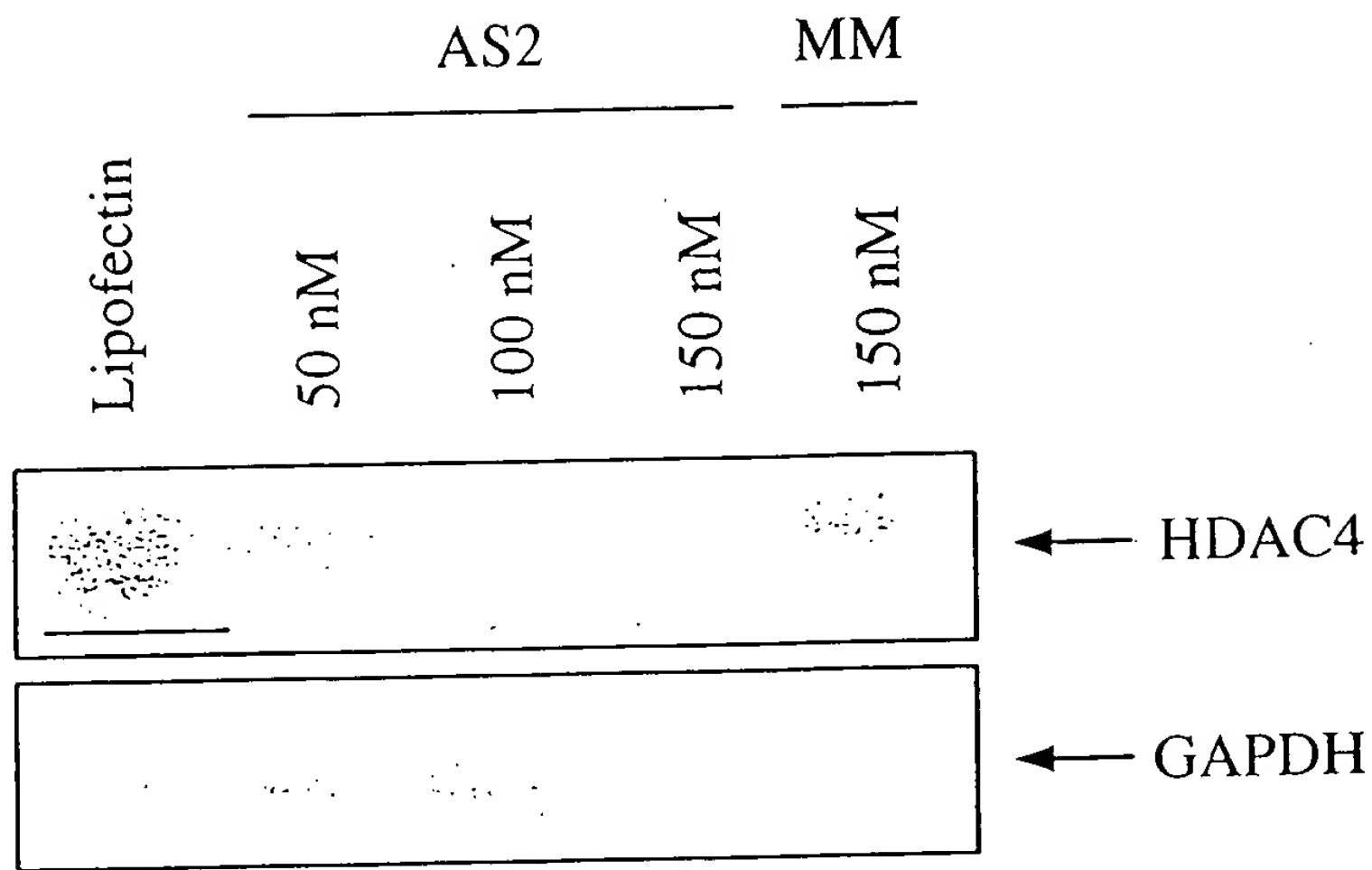


FIG. 9F ~~1F~~

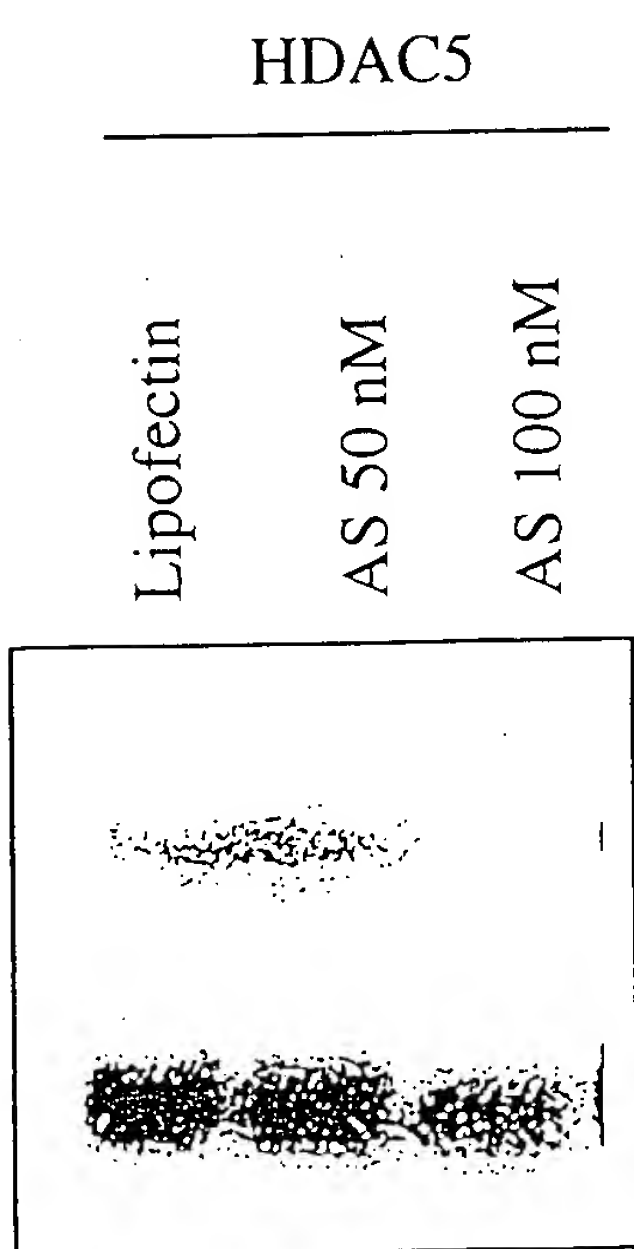


FIG. 9G ~~1G~~

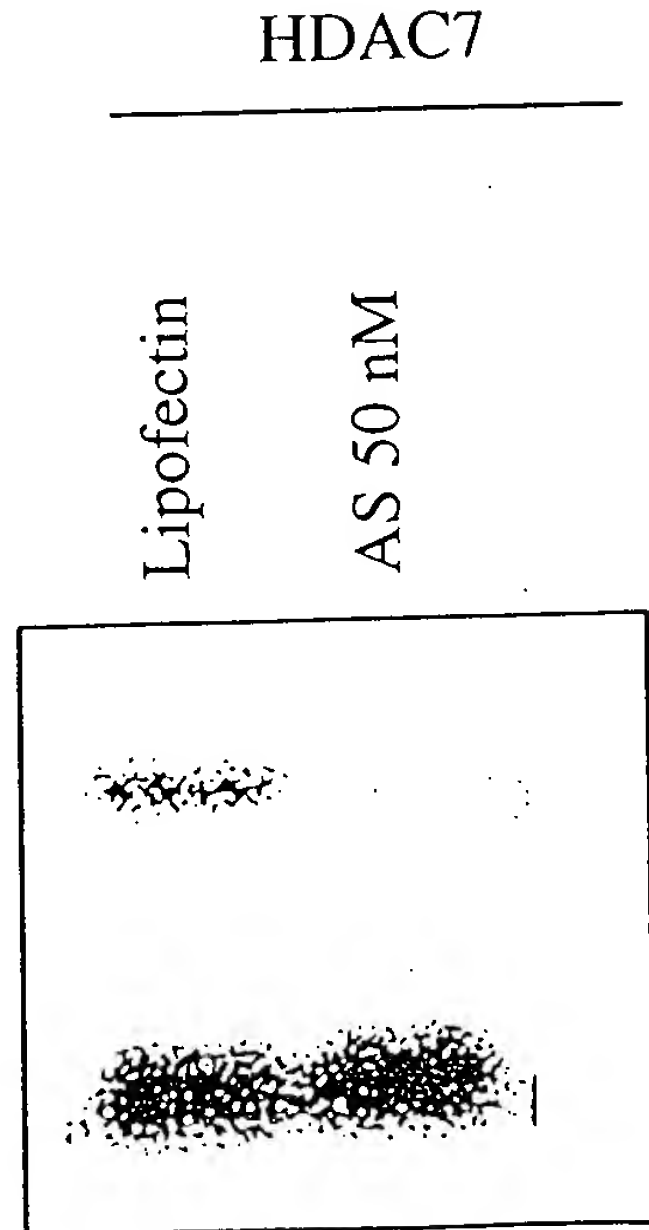


FIG. 9H ~~1H~~

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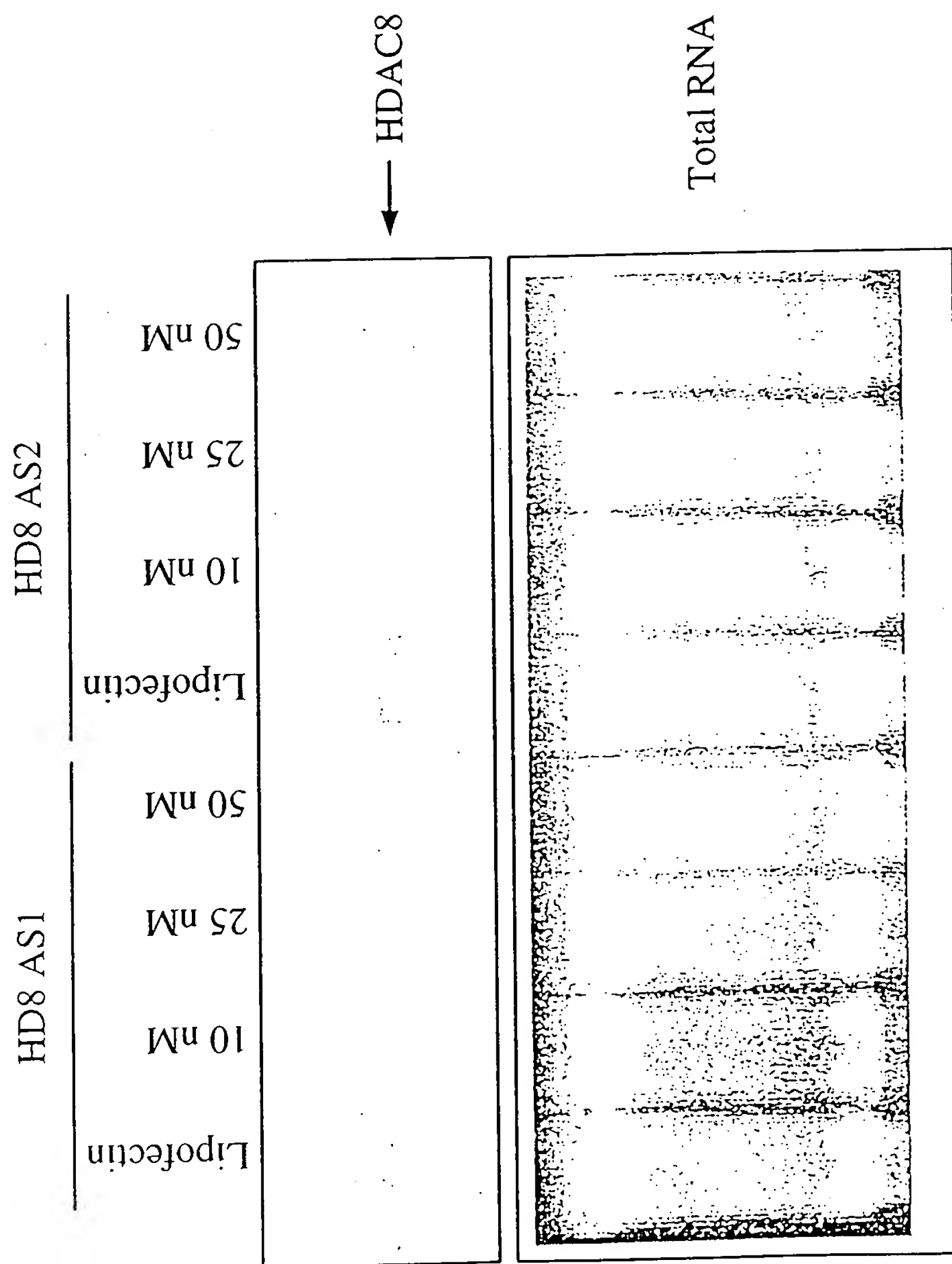
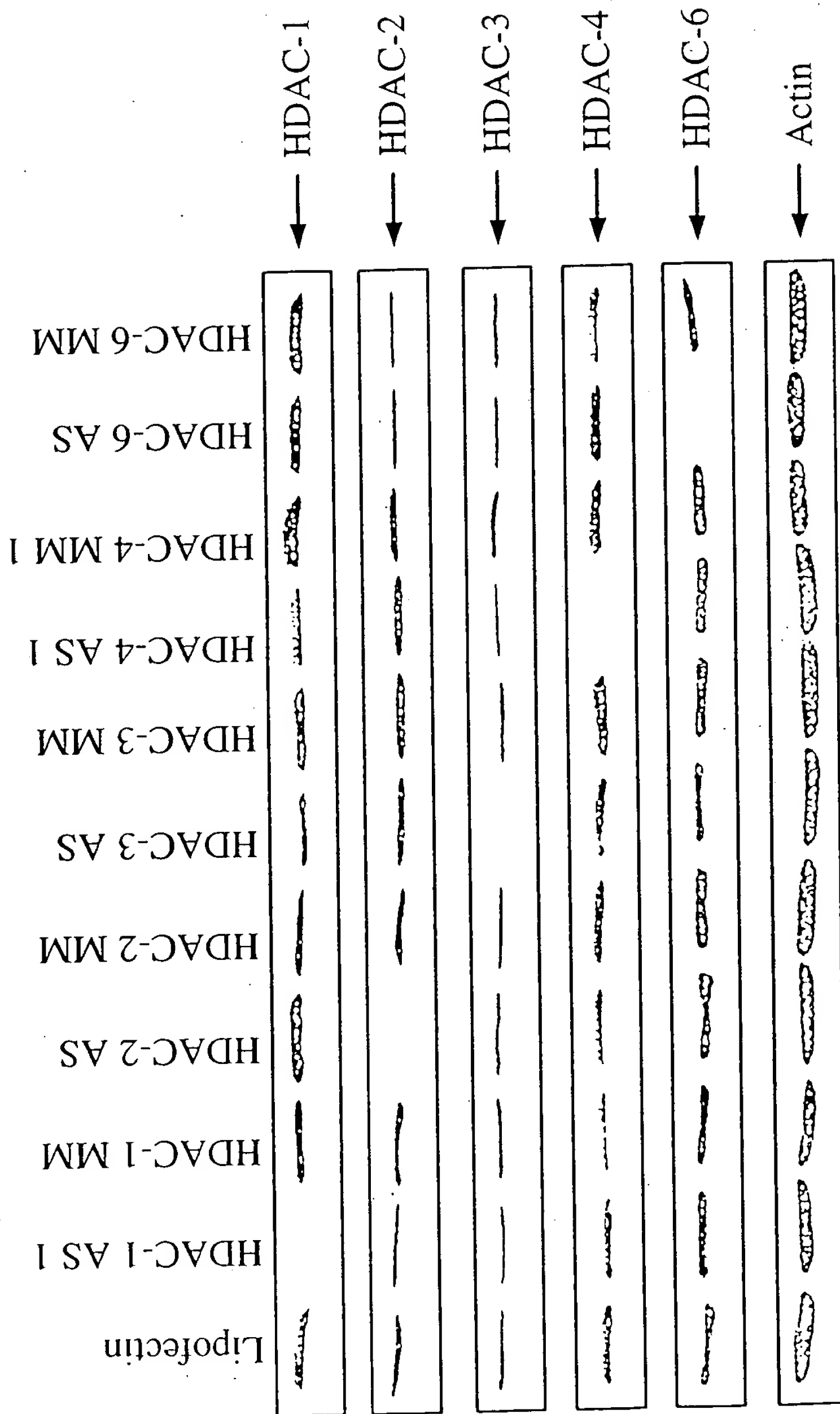


FIG. 9I

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AS = Antisense
MM = Mismatch
NS = Non-specific control
3 day treatment
Oligonucleotide cone – 50nM

FIG. 10A 2A

~~30/37~~ 6/13

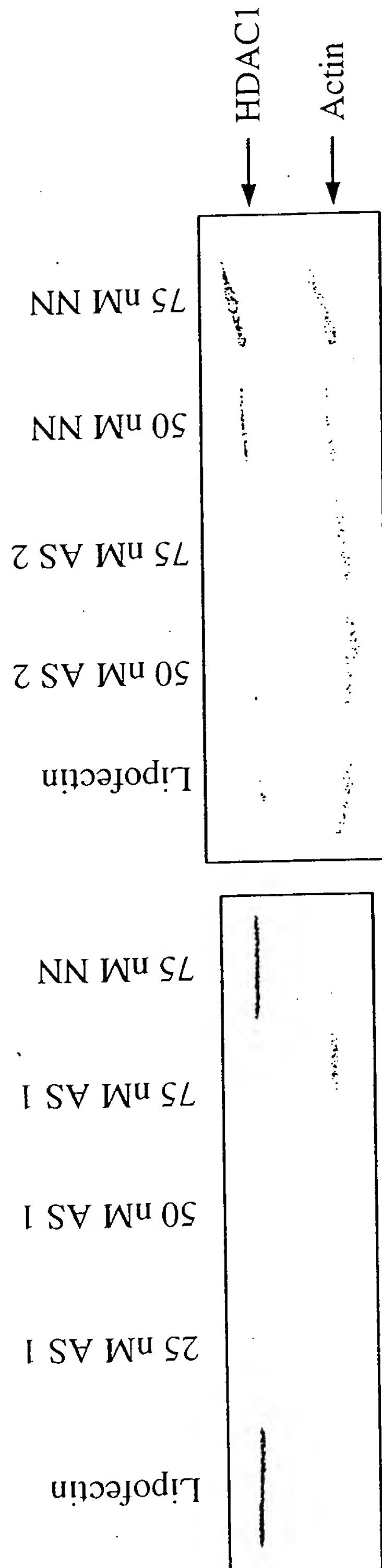


FIG. 40B-2B

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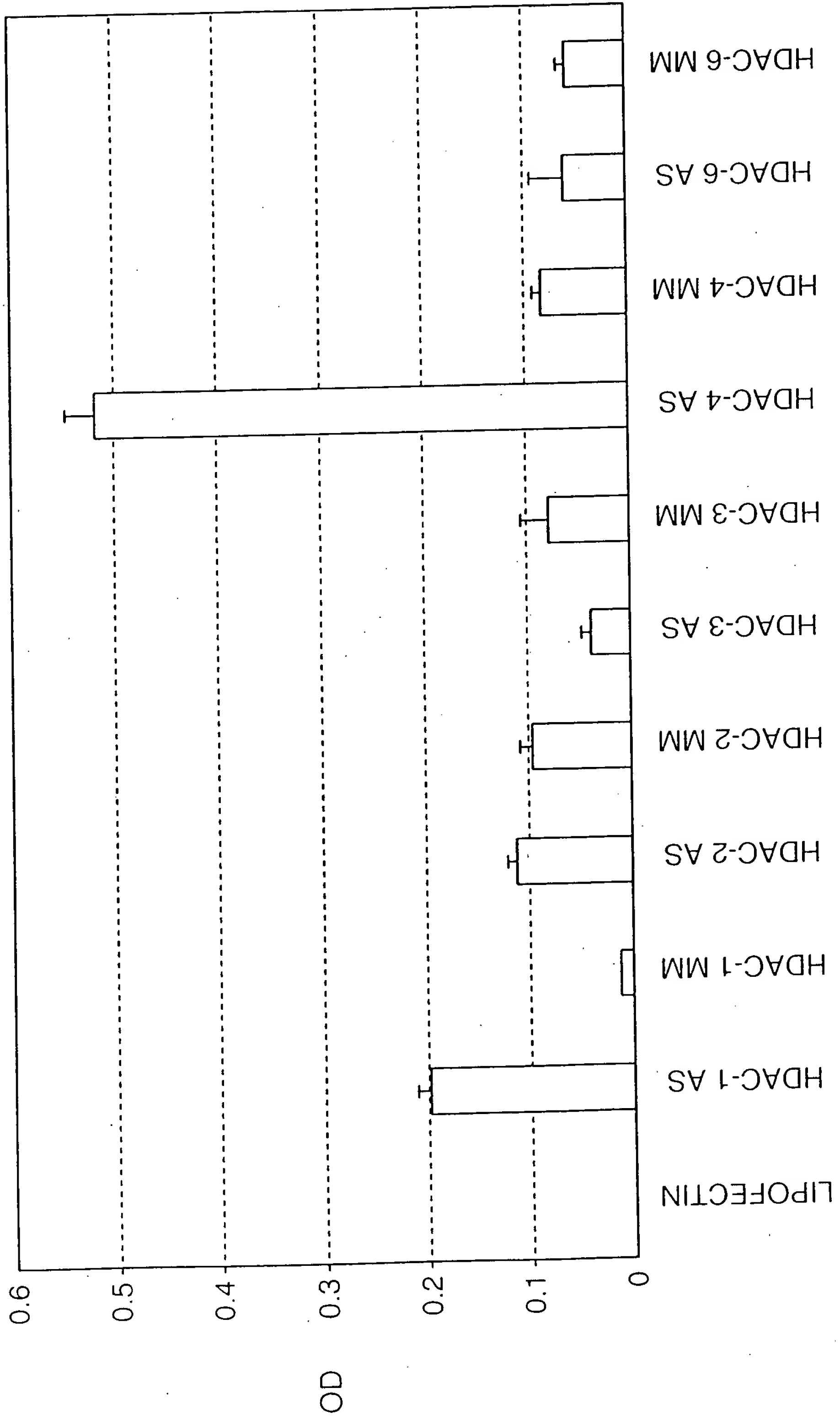


FIG. 113

~~32/37~~ 8/13

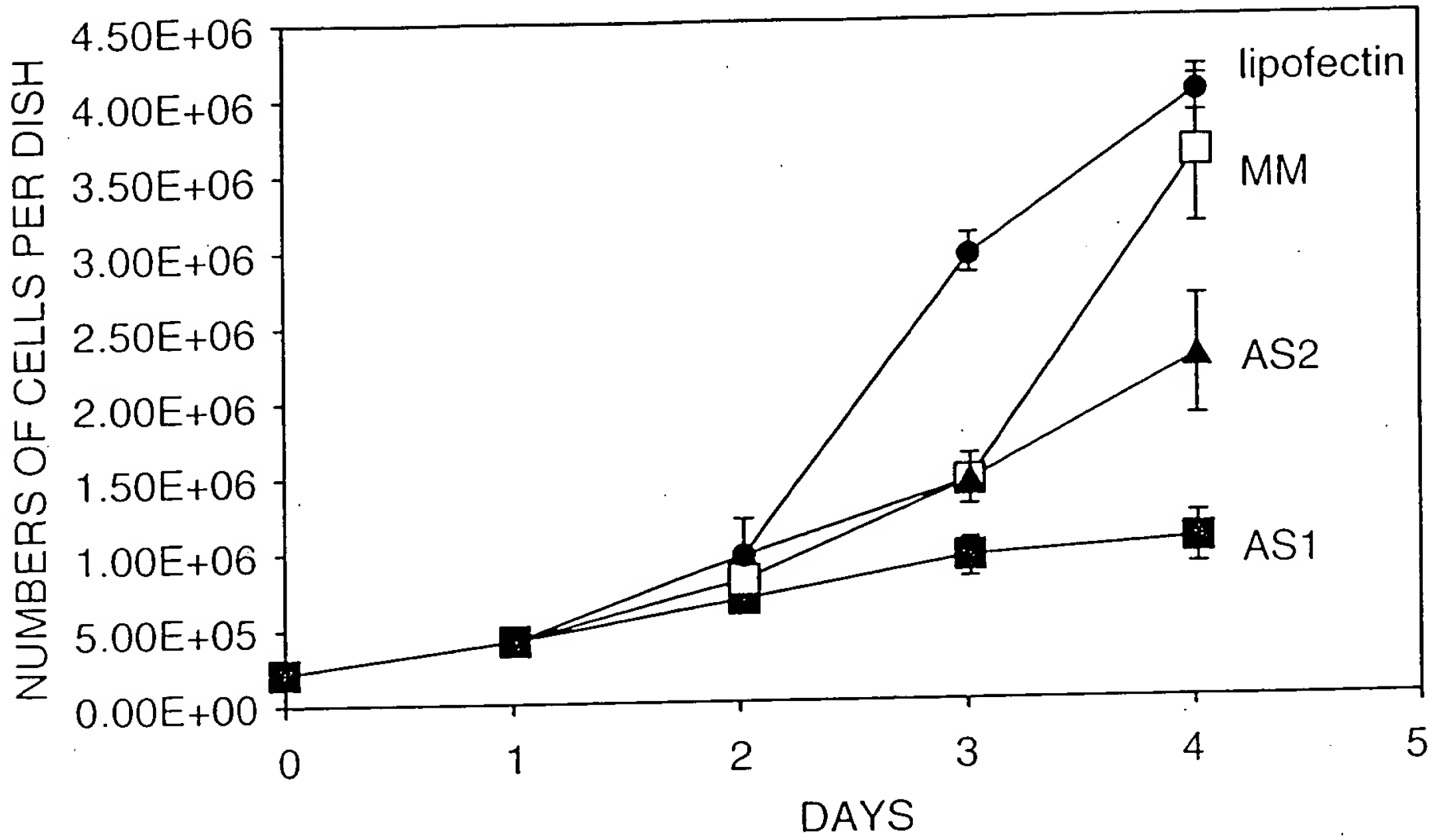


FIG. ~~12A~~ 4A

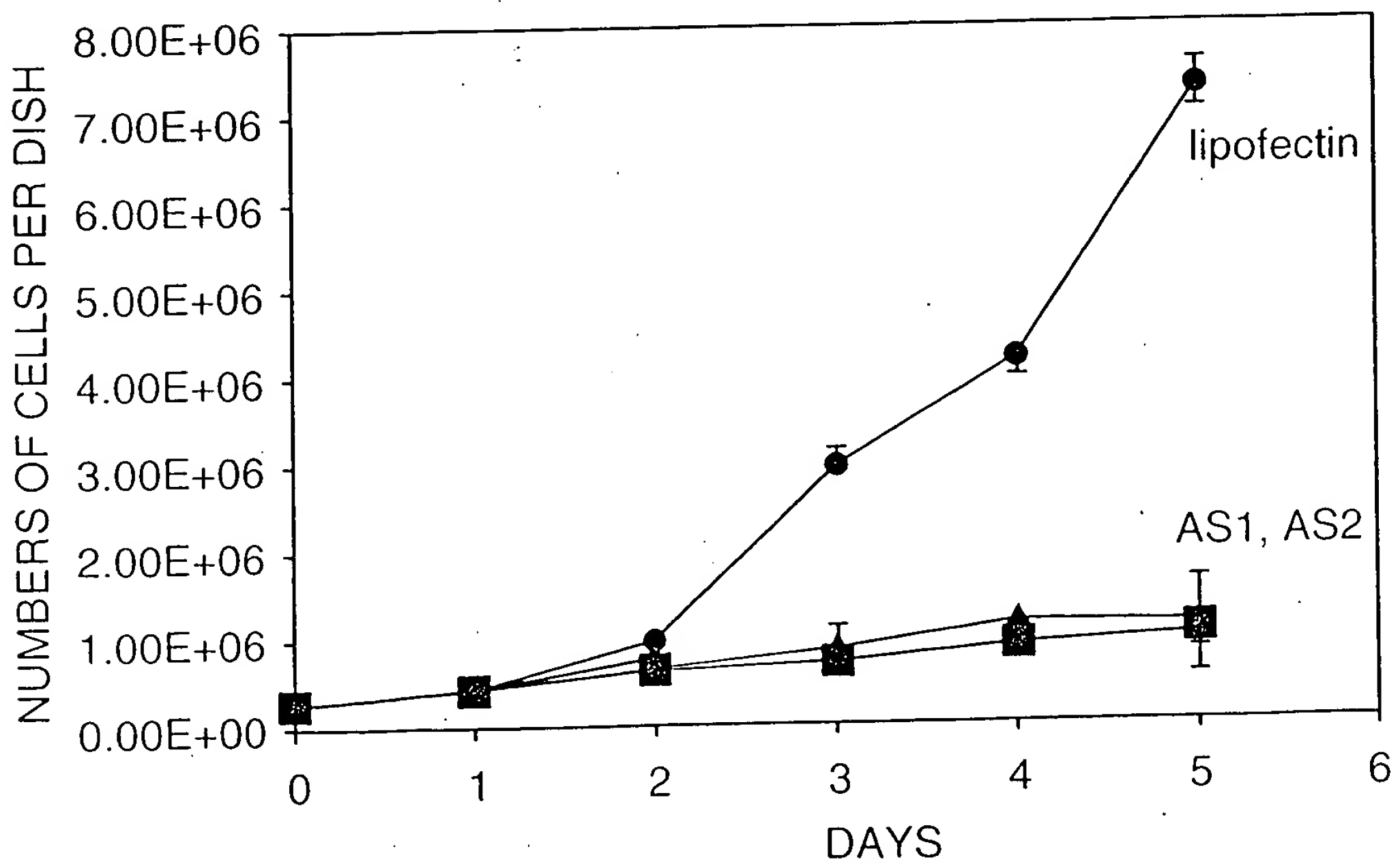


FIG. ~~12B~~ 4B

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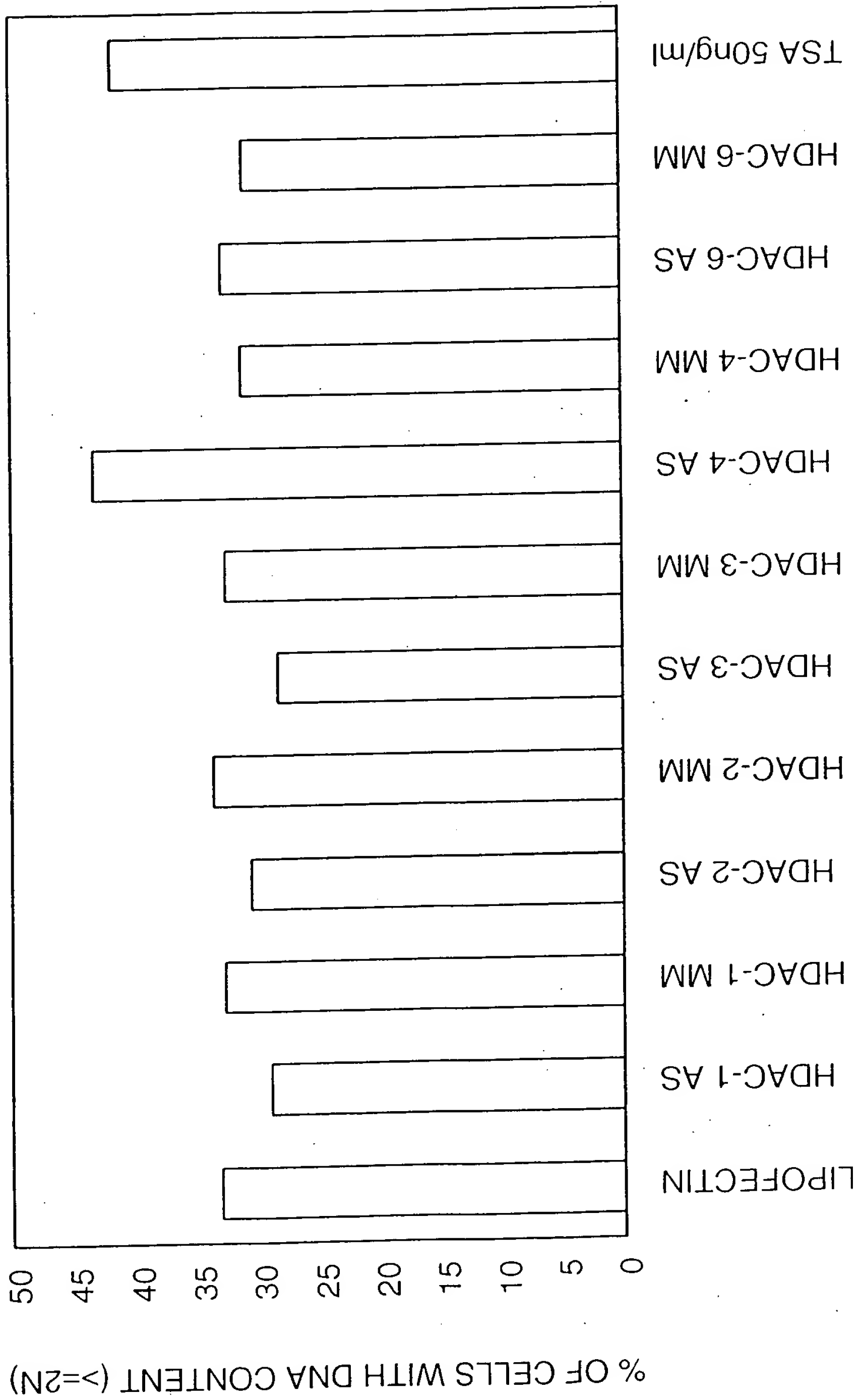


FIG. 13-5

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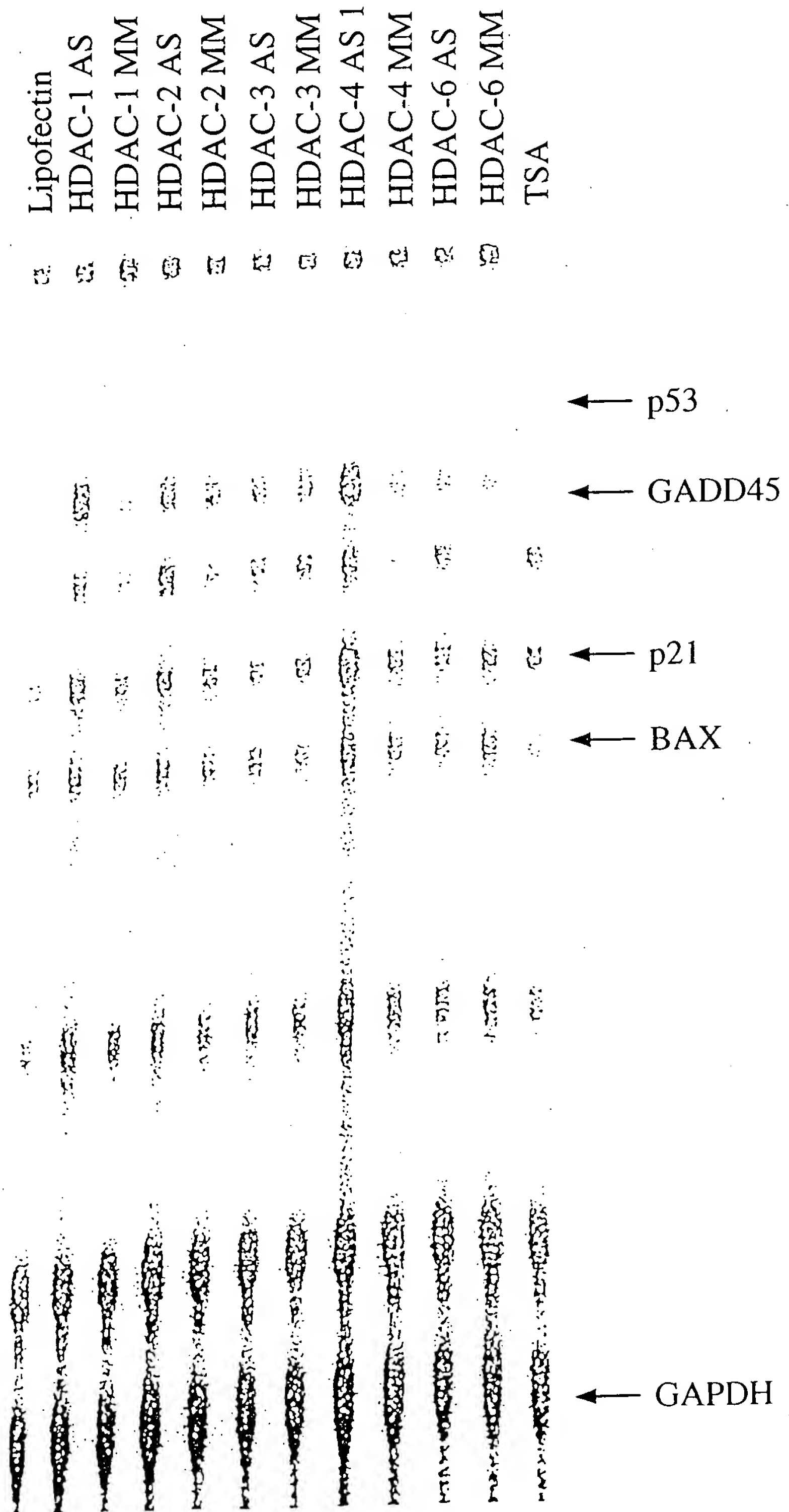


FIG. 14 b

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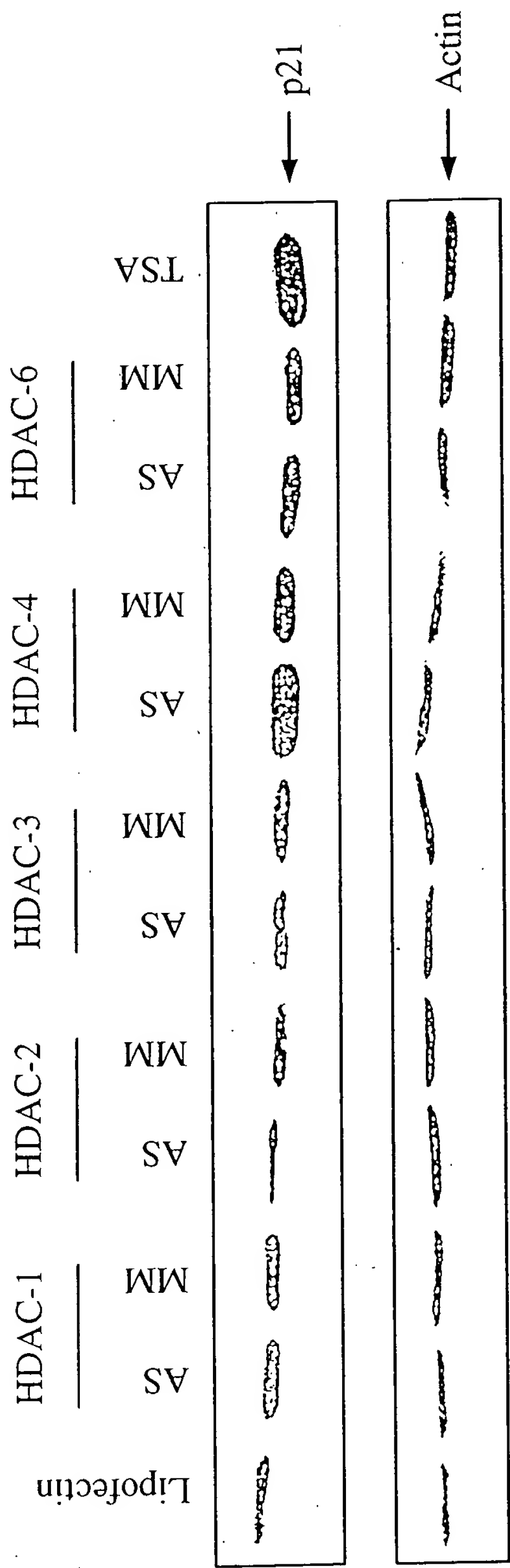


FIG. 15 7

~~36/37~~ 12/13

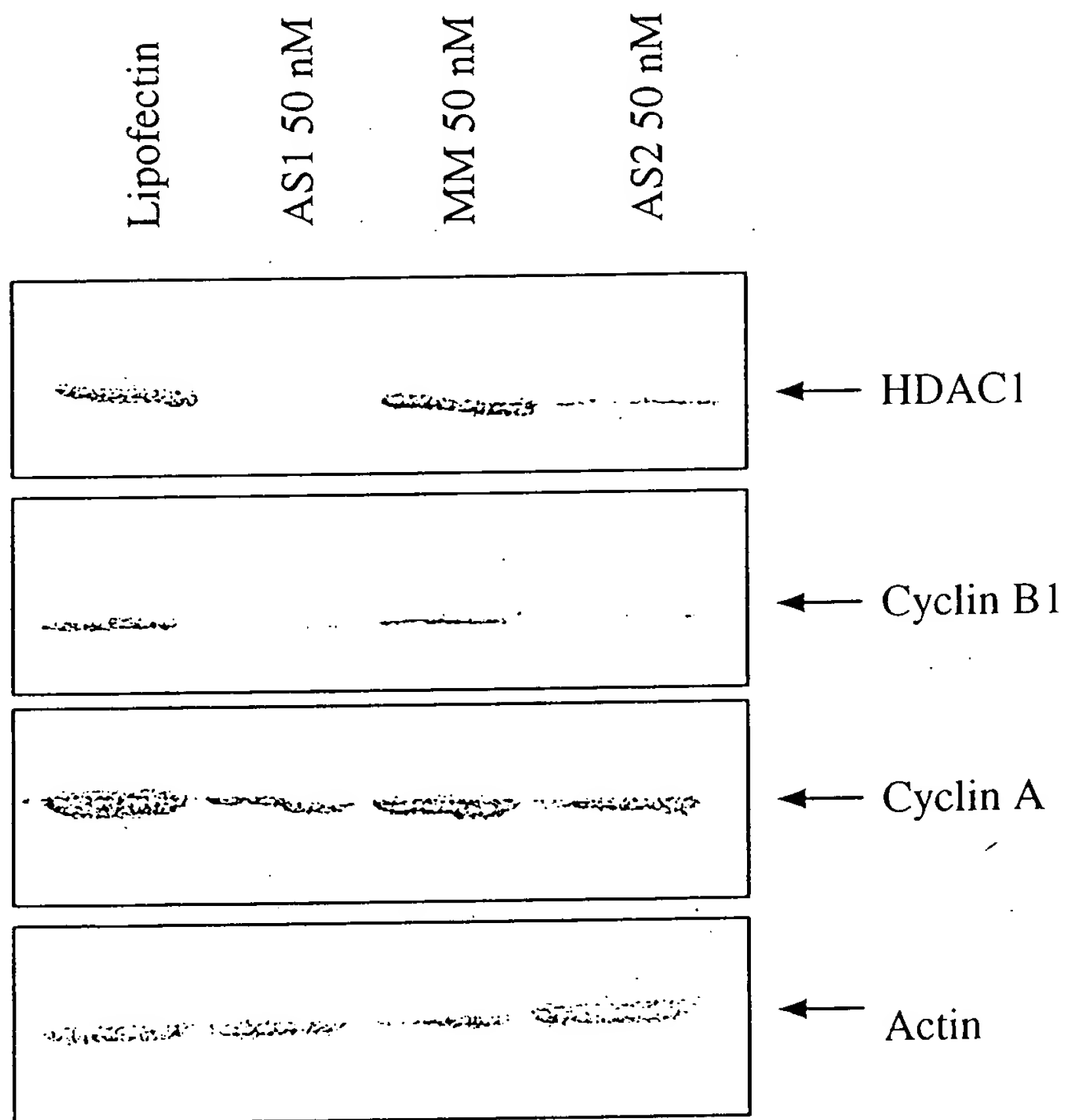
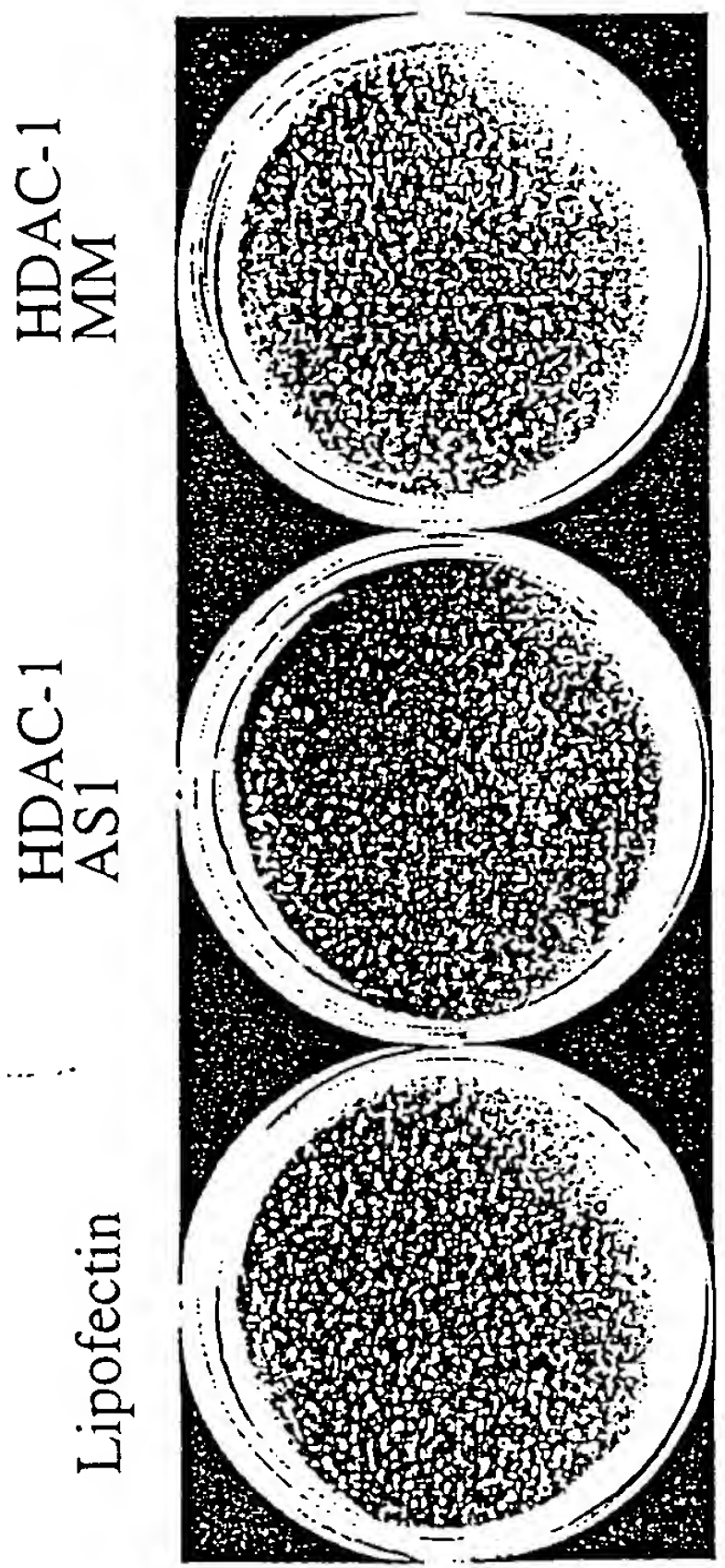
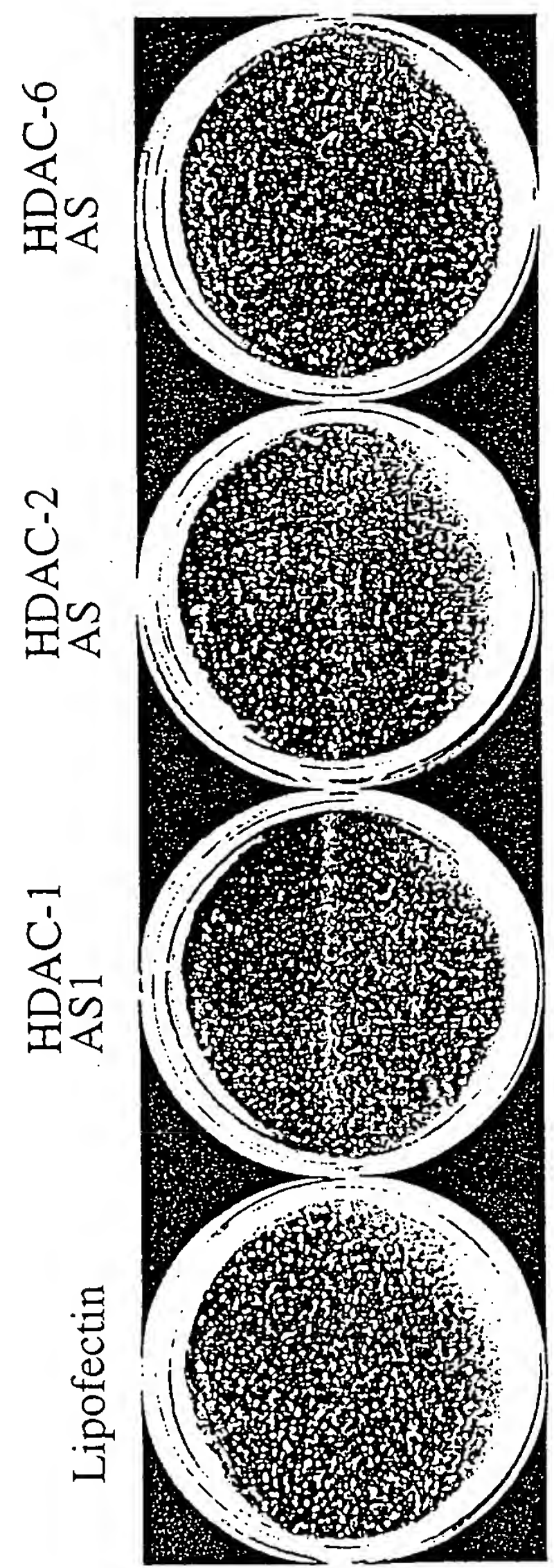


FIG. 16-8

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Colony Numbers -1200 -120 -1160
FIG. 17A 9A



Colony Numbers -1200 -120 -890 -730
FIG. 17B 9B